Individualization of drug therapy considering pharmacokinetic and clinical factors

Dissertation zur Erlangung des
naturwissenschaftlichen Doktorgrades
der Julius-Maximilians-Universität Würzburg

vorgelegt von
Martin Reinhold Munz

aus Gaildorf

Würzburg 2018

Eingereicht bei der Fakultät für Chemie und Pharmazie am

_____

Gutachter der schriftlichen Arbeit

1. Gutachter: Prof. Dr. Fritz Sörgel

2. Gutachter: Prof. Dr. Ulrike Holzgrabe

Prüfer des öffentlichen Promotionskolloquiums

1. Prüfer: _____

2. Prüfer: _____

3. Prüfer: _____

Datum des öffentlichen Promotionskolloquiums

_____

Doktorurkunde ausgehändigt am

_____

Die vorliegende Arbeit wurde am IBMP - Institut für Biomedizinische und Pharmazeutische Forschung in Nürnberg-Heroldsberg angefertigt.

This thesis has been accomplished at the IBMP - Institute for Biomedical and Pharmaceutical Research in Nürnberg-Heroldsberg.

Für meine Familie

Acknowledgement

This thesis has been accomplished under the supervision of Professor Dr. Fritz Sörgel, IBMP - Institute for Biomedical and Pharmaceutical Research in Nürnberg-Heroldsberg, and Professor Dr. Ulrike Holzgrabe, Department of Pharmaceutical Chemistry, University of Würzburg, Germany.

First and foremost, I greatly thank Professor Dr. Sörgel for the assignment of the scientific topic for this Ph.D. thesis, for his continuous support, advice and guidance during this thesis and for the opportunity of working on fascinating clinical projects in collaboration with the Department of Hematology and Oncology and the Department of Anesthesiology and Intensive Care Medicine of the Paracelsus Medical University, Nürnberg, Germany, and the Department for Trauma Surgery, University of Erlangen, Germany.

My warmest thank you goes to Professor Dr. Ulrike Holzgrabe for supporting this Ph.D. thesis, providing feedback and guiding together with Professor Dr. Sörgel the direction and progress of this work.

My warmest thank you also goes to Professor Dr. Martin Wilhelm and PD Dr. Joseph Birkmann who let me participate on their medical rounds, supported me and gave me advice in our clinical projects. Moreover, I am very thankful for the inclusion into the staff of the Department of Hematology and Oncology of the Paracelsus Medical University, Nürnberg.

I am very thankful to Christoph Stelzer, Dr. Martina Kinzig, and the whole laboratory team of the IBMP who did the analysis of the clinical samples.

I thank Dr. Jürgen Bulitta for his support in analyzing the pharmacokinetic and pharmacodynamic data of meropenem and imipenem / cilastatin and I thank my colleague Rebekka Glaser for proofreading my manuscripts.

In addition, I wish to address my thanks to all my colleagues and friends at the IBMP and the Department of Hematology and Oncology who made the time of my Ph.D. work unforgettable.

Publications

Full papers:

1. Djukic M, Munz M, Sörgel F, Holzgrabe U, Eiffert H, Nau R: Overton's rule helps to estimate the penetration of anti-infectives into patients' cerebrospinal fluid. Antimicrob Agents Chemother. 2012;56:979-88.
2. Sörgel F, Munz M: "Mut zur Wut" Die e-Zigarette und das Für und Wider, ob Nicotin ein Arzneimittel ist. Deutsche Apotheker Zeitung. 2012;10:1218-1226.
3. Munz M: Prävention und Management unerwünschter Arzneimittelwirkungen - Hochdosistherapie mit Methotrexat. Österreichische Apotheker Zeitung. 2016;8:52-56 und 2016;9:45-48.
4. Sörgel F, Höhl R, Glaser R, Stelzer C, Munz M, Vormittag M, Kinzig M, Bulitta J, Landersdorfer C, Junger A, Christ M, Wilhelm M, Holzgrabe U: Pharmakokinetik und Pharmakodynamik von Antibiotika in der Intensivmedizin. Med Klin Intensivmed Notfmed. 2017;112:11-23.
5. Munz M, Grummich H, Birkmann J, Wilhelm M, Holzgrabe U, Sörgel F. Severe Drug-Induced Liver Injury as an Adverse Drug Event of Antibiotics: A Case Report and Review of the Literature. Chemotherapy. 2017;62(6):367-373.
6. Munz M, Pretscher D, Wilhelm M, Holzgrabe U, Sörgel F, Birkmann J: Azathioprine-induced reversible EBV-associated Hodgkin-like lymphoma after immunosuppressive therapy for autoimmune hepatitis. Int J Clin Pharmacol Ther. 2018;56:142-147.

Congress presentations:

1. Munz M, Wilhelm M, Schlosser D, Birkmann J, Kinzig M, Holzgrabe U, Sörgel F: Evaluation of the benefits of pharmaceutical care in a department for hematology and oncology by a clinical pharmacist. Poster PO-189, Joint Meeting of the Austrian and German Pharmaceutical Societies (Österreichische und Deutsche Pharmazeutische Gesellschaft, ÖPhG und DPhG); Innsbruck, Austria; September 20 - 23, 2011.
2. Sörgel F, Munz M, Djukic M, Eiffert H, Kinzig M, Holzgrabe U, Nau R: Overton`s rule helps to estimate the penetration of anti-infectives into the cerebrospinal fluid. Poster PO-194, Joint Meeting of the Austrian and German Pharmaceutical

Societies (Österreichische und Deutsche Pharmazeutische Gesellschaft, ÖPhG und DPhG); Innsbruck, Austria; September 20 - 23, 2011.

3. Wilhelm M, Munz M, Birkmann J, Link K, Kinzig M, Holzgrabe U, Sörgel F: PEAK part I – a comprehensive program to personalize and optimize drug treatment by pharmacokinetics. Paracelsus Science Get Together 2012; Salzburg, Austria; June 29, 2012.
4. Wilhelm M, Munz M, Birkmann J, Link K, Kinzig M, Holzgrabe U, Sörgel F: PEAK part II – reducing drug adverse events and drug interactions by using the iPad. Paracelsus Science Get Together 2012; Salzburg, Austria; June 29, 2012.
5. Munz M, Grummich H, Birkmann J, Wilhelm M, Holzgrabe U, Sörgel F: Severe Drug-induced Liver Injury as Adverse Drug Event of Antibiotics - Case Report and Review of the Literature. Paracelsus Science Get Together 2014; Salzburg, Austria; June 27, 2014.
6. Glaser R, Munz M, Stelzer C, Kinzig M, Braun T, Hüttner S, Wilhelm M, Holzgrabe U, Sörgel F: New Insights Into the Pharmacokinetics of Cytarabine by a New Highly Sensitive Mass Spectrometric Assay in Patients With Hematologic Neoplasms. Paracelsus Science Get Together 2014; Salzburg, Austria; June 27, 2014.
7. Stelzer C, Kinzig M, Lam MH, Wolferstetter E, Krinner S, Munz M, Hennig F, Ogilvie A, Holzgrabe U, Sörgel F: Challenges in Analyzing Endogenous and Foreign Compounds in Bone Tissue by Tandem Mass Spectrometry. Paracelsus Science Get Together 2014; Salzburg, Austria; June 27, 2014.
8. Riccobene T, Cole P, Wolferstetter E, Munz M, Stelzer C, Krinner S, Kinzig M, Hennig F, Holzgrabe U, Sörgel F: Penetration of Ceftaroline (CPT) into Bone Following Administration of Ceftaroline Fosamil (CPT-F) to Subjects Undergoing Total Hip Replacement Surgery. Poster A-1333, 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); Washington, DC; September 5 - 9, 2014.
9. Munz M, Bulitta JB, Höhl R, Jensen A, Junger A, Glaser R, Stelzer C, Kinzig M, Bertsch T, Holzgrabe U, Sörgel F: Individualizing meropenem prolonged infusions in intensive care unit patients via population modeling of renal function and infection biomarkers over time. Paracelsus Science Get Together 2015; Nürnberg, Germany; July 3, 2015.

10. Glaser R, Stelzer C, Wilhelm M, Munz M, Kinzig M, Bulitta J, Holzgrabe U, Sörgel F: First Report on Very Long Terminal Half-Life of Cytarabine in Patients with Hematological Malignancies Assessed via Population Pharmacokinetics. Poster R6293. 2015 AAPS Annual Meeting and Exposition; Orlando, Florida; Oct. 25-29, 2015.

Table of contents

List of figures

List of tables

1. Introduction

1.1. Background

The „Position Paper of the Division of Clinical Pharmacy of the German Pharmaceutical Society (DPhG)" defines clinical pharmacy as the science and practice of the rational use of drugs[1], which includes the individualization of drug therapy. The individualization of drug therapy can be defined as "tailoring drug selection and drug dosing to a given patient" with the purpose to optimize the benefit and minimize the harm of therapeutic interventions on a patient-by-patient basis[2].

An increasing number of studies show that the "one size fits all" approach is outdated and a large proportion of patients may benefit from dose individualization[3]. However, for numerous drugs, individualization of pharmacotherapy is restricted by lacking information concerning altered pharmacokinetics in patients, who are differing in demographical (age[4], sex[5], weight[6], etc.), physiological or clinical data (organ function[7], disease stage[8], concomitant medications[9], etc.) or lifestyle habits[10] (smoking status, etc.) from the "average adult patient", who is included in modern registration trials. As might be expected, the situation for drugs that have been in use for decades is similar, as the pharmaceutical industry has little interest in conducting sophisticated and expensive pharmacokinetic trials for drugs that are available as generics.

The limited data concerning dose individualization is reflected by the fact that prescribing informations of numerous drugs provide only insufficient or even no information about dose adjustment in special patient populations. Table 1-1 illustrates this lack of information for anti-infective and antineoplastic drugs. As a result, the vast majority of drugs have "one-size-fits-all" dosing that is usually derived from clinical trials of phase II, which generally include only a limited number of patients and exclude patients with particular patient characteristics.

As a result, investigations on pharmacokinetic factors and clinical factors influencing drug therapy and in particular dosing of drugs may provide a significant contribution for the individualization and therefore optimization of pharmacotherapy.

Table 1-1 Available information concerning dose adjustments and pharmacokinetic changes for specific patient populations in the German prescribing information.
(Accessed April 27, 2018)

	Renal impairment	Hepatic impairment	Obesity	Geriatric	Genetically determined metabolism	Sex
ampicillin[11,12]	x	-	-	-	-	-
cefotaxime[13]	x	-	-	x	-	-
cefuroxime[14]	x	x	-	x	-	x
clarithromycin[15]	x	- (1)	-	x	-	-
clindamycin[16]	x (2)	x (2)	-	x	-	-
cotrimoxazole[17]	x	x	-	-	-	-
daptomycin[18]	- (3)	- (1)	x	x	-	x
fluconazole[19]	x	- (4)	-	x	-	-
linezolid[20]	x (5)	- (1)	-	x	-	x
metronidazole[21]	x (5)	x	-	- (6)	-	-
moxifloxacin[22]	-	- (4)	-	x	-	-
piperacillin[23]	x	x	-	x	x	-
roxithromycin[24]	x (7)	x (7)	-	x	-	-
sulbactam-sodium[12]	x	-	-	-	-	-
dasatinib[25]	x	x	-	x	-	-
everolimus[26]	x	x	-	x	x	-
gefitinib[27]	- (3)	x	x	x	x	x
gemcitabine[28]	- (3)	- (4)	-	x	-	x
lapatinib[29]	- (8)	- (4)	-	- (6)	-	-
lenalidomide[30]	x	- (4)	x (9)	x	x	x
nilotinib[31]	- (8)	x (4)	-	x	-	-
paclitaxel[32]	-	- (4)	-	-	-	-
pazopanib[33]	- (8)	x	-	- (6)	-	-
sorafenib[34]	x (10)	- (1)	x	x	x	x
sunitinib[35]	x	- (1)	-	x	-	x

(1) No data on patients with severely impaired hepatic function.
(2) Clindamycin concentrations should be monitored in patients with severely impaired kidney or liver function.
(3) Limited data in patients with (severely) impaired renal function.
(4) Limited data on patients with (severely) impaired hepatic function.
(5) Metabolites were not considered.
(6) Limited data on geriatric patients.
(7) Roxithromycin concentrations should be monitored in patients with severely impaired renal and liver function.
(8) No data on patients with severely impaired renal function.
(9) No date on patients > 135kg.
(10) No data on patients undergoing dialysis.

1.2. Pharmacokinetics

Pharmacokinetics may be defined as what the body does to a drug[36]. Pharmacokinetics describe the time course of a drug into, through, and out of the body and therefore the absorption, distribution, metabolism, and excretion of a drug. This processes are combined in the term “ADME-scheme” and every of this processes can be described mathematically by means of the pharmacokinetic variables “clearance (CL)”, “volume of distribution (Vd)”, “area under the curve (AUC)”, “elimination rate constant (ke)”, “maximum or peak plasma concentration (Cmax)” and the “time at which the Cmax is observed (t_{max})”.

1.2.1. Clearance (CL)

The clearance (CL) determines the removal of drug from the body. CL is expressed as volume per time and therefore indicates a hypothetical volume of fluid in the body, which is completely cleared from the drug in a defined time interval. CL therefore represents a volume that is “cleared” from a substance and not the amount of substance that is eliminated. The total body clearance (CL_T) is the sum of all processes in the body, which take part in removing a substance of the body or simplified, CL_T is the sum of renal excretion processes (CL_R) and nonrenal processes (CL_{NR}), as described by the equation:

$$CL_T = CL_R + CL_{NR} \qquad \textit{Equation 1}$$

1.2.2. Volume of distribution (Vd)

The term “volume of distribution” (Vd) is a hypothetical construct and refers to the size of a compartment necessary to account for the total amount of the drug in the body, making the assumption that its concentration in the whole body is equal to the concentration measured in blood (or serum or plasma). As the blood concentration of a drug is proportional to the volume of distribution in general, the larger the volume of distribution, the larger a dose must be to achieve the targeted concentration. Vd is therefore an important parameter for the determination of adequate dosing regimens.

Vd of a drug can be determined by bolus administration of a defined dose of this drug and measurement of the peak concentration (Cmax). With this information, Vd can be calculated by the equation:

$$Vd = \frac{Dose}{c_{\max}}$$ *Equation 2*

Dependent on the use of non-compartmental or compartmental analysis for the determination of Vd, the terminal phase volume (V_Z) or steady state volume (V_{SS}) is obtained. If compartmental analysis is based on one compartment, V_Z equals V_{SS}. However, for all other cases V_Z might be misleading[37], as V_Z is affected by variation of clearance and ke, as apparent from equation 3 (see below).

1.2.3. Elimination rate constant (ke) and half-life ($t_{1/2}$)

The elimination rate constant (ke) describes the rate, at which a substance is eliminated from the body. In first order kinetics, ke can be determined as the negative slope of the terminal phase of a semi-logarithmic plot of the concentration time profile of a drug. ke can also be described as a function of CL and Vd:

$$ke = \frac{CL}{Vd}$$ *Equation 3*

The corresponding half-life ($t_{1/2}$) of a given substance, which has first order kinetics, can be determined by the equation:

$$t_{1/2} = \frac{\ln(2)}{ke}$$ *Equation 4*

1.2.4. Area under the curve (AUC)

The area under the plasma concentration over time curve (AUC) represents the total exposure of an individual to the drug within one dosing interval (T).

The most common way to calculate the AUC is the trapezoidal method (trapezoidal rule). When calculating the AUC using the trapezoidal rule, the overall area is divided in a number of trapezoids and their individual area is calculated. The overall area is calculated as the sum of all trapezoid areas.

If dosage and clearance of the drug are known, the AUC can also be calculated by using the following equation:

$$AUC = \frac{Dose}{Cl}$$ *Equation 5*

1.3. Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS)

Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) is a combination of two analytical methods with different underlying principles. LC-MS/MS provides very high sensitivity and selectivity and is therefore a frequently used method for the bioanalytical determination of drug concentrations in complex matrices as biological specimens.

1.3.1. Liquid chromatography (LC)

The analytical principle of liquid chromatography (LC) is the chromatographic separation of the sample into single components.

Fundamental elements of LC are a sample in dissolved state, a liquid mobile phase and a stationary phase. In modern LC, which is referred to as HPLC “high performance liquid chromatography” or UHPLC “ultra-high performance liquid chromatography”, the stationary phase consists of very small particles (3 to 5 µm in diameter in HPLC and even less in UHPLC), which are packed into a column. Due to the dense packing of these small particles, high pressure is needed to force the liquid mobile phase trough the column. HPLC is therefore sometimes also referred to as “high pressure liquid chromatography”.

The chromatographic separation is based on the different partition of the individual components of the sample in the mobile and the stationary phase and the underlying differences in the individual affinity for the two phases. If the stationary phase is more polar than the mobile phase, the chromatography is referred to as “normal phase”, and if the mobile phase is more polar than the stationary phase, the chromatography is referred to as “reversed phase”.

Depending on the different partition between the two phases, the individual components of a sample elute at different times from the column and can be detected separately. However, LC itself cannot detect and quantify substances and has therefore always to be coupled with a method, which is capable to detect and quantify substances.

1.3.2. Mass spectrometry (MS)

Mass spectrometry (MS) is an analytical method that separates ions according to their mass-to-charge ratio (m/z) in the gas-phase. MS is therefore based on physical principles and can be used to a) identify and b) quantify chemicals present in a sample.

MS takes place in a high vacuum, because otherwise neither a permanent ionization nor undisturbed and focusable ion beams arise[38]. The three main components of a mass spectrometer are an ion source, which ionizes the analyte and other molecules of the sample, a mass analyzer, which sorts the ions by their m/z ratio, and a detector, which records ions passing by or hitting a surface.

In MS, a number of ionization techniques are in use, depending on the phase (solid, liquid, gas) of the sample, the analyte molecule and the required efficacy of ionization. In LC-MS, the sample consists of charged ions and charged and / or neutral components of the mobile phase and of the solvent. The most common ion source for this application is the Electrospray Ionization (ESI) technique. This ionization method is considered a soft ionization, as ESI does not cause the ions to fragment.

The ESI-interface consists of a metal capillary, were an electrical voltage is created and the analyte solution is passed through. The resulting spray consists of droplets, which are de-solvated by a combination of temperature, vacuum and acceleration into gas by voltages[39]. The voltage, which is applied to the capillary, determines the charge of the ions that are generated. A positive voltage generates positively charged ions and a negative voltage generates negatively charged ions. Because of the natural use of a flowing liquid, ESI is easily adapted to liquid chromatography (LC).

The most common method in LC-MS for the separation of ions with different m/z ratios is the quadrupole technique. Here, high frequency electric fields are generated by means of four rod electrodes, which stimulate the ions to oscillating trajectories. These fields can be adjusted to allow only ions of a specific m/z ratio to pass the mass filter.

The detector records ions, which have passed the mass filter. As the number of ions passing the mass filter at a particular time is very small, amplification of this signal is needed, for example by an electron multiplier. Finally, the signal is plotted against the mass to charge ratio by a computer.

1.3.3. Tandem mass spectrometry (MS/MS)

The selectivity of MS can be increased by using a linear series of three quadrupoles. In this series, the first and the third quadrupole are used as mass analyzers, while the quadrupole in the middle is used as a collision cell. In this collision cell, the parent ions from the first quadrupole are fragmented using an inert gas for collision. The resulting specific product-ions can then be selected by the third quadrupole.

1.4. Overall aim of this thesis

The overall aim of this thesis was to determine pharmacokinetic factors and clinical factors that make an individualized approach of pharmacotherapy sensible and necessary. Against this background, the thesis was divided into seven separate chapters describing clinical and pharmacokinetic factors that have a direct impact on pharmacotherapy.

As clinical factor, “critical illness” was selected. Two chapters provide an overview of literature data of pharmacokinetic studies for the carbapenem antibiotics imipenem and meropenem in critically ill patients and compare these results with literature data of healthy volunteers. Another two chapters describe the establishment of a therapeutic drug management (TDM) program for antibiotics in a surgical intensive care unit and study the pharmacokinetics of imipenem / cilastatin and meropenem in this population of patients.

As pharmacokinetic factor, the “bone penetration” of ampicillin and sulbactam was investigated. Therefore, the pharmacokinetics of ampicillin and sulbactam in plasma and bone tissue in patients undergoing total hip replacement surgery with perioperative antibiotic prophylaxis were studied.

As clinical factors related to the individual patient, two case reports demonstrate the occurrence of rare adverse events of drugs as a result of (unknown) predisposition of the individual patient.

2. Overview of pharmacokinetic studies of imipenem / cilastatin in critically ill patients and healthy volunteers

2.1. Introduction

2.1.1. Background

Infection and related sepsis are the leading cause of morbidity and death in non-cardiac intensive care units (ICUs). In-hospital mortality of 29.7 % was found in a recent retrospective analysis of a large dataset collected prospectively for the Surviving Sepsis Campaign[40]. Other authors even reported sepsis related mortality rates up to 60 % in non-cardiac ICUs and sepsis related costs that account for approximately 40 % of total ICU expenditures[41].

Appropriate antibiotic initial therapy remarkably decreases the mortality of patients with infections in the ICU[42]. As antibiotic treatment is empirical in this setting and starts before the results of microbiological testing are known, the first-line therapy should cover a broad spectrum of Gram-negative and Gram-positive bacteria and should be adapted to the current resistance situation[43].

Due to their large antimicrobial spectrum and low toxicity, the beta-lactam antibiotics are among the first-line therapies for critically ill patients, especially when a Gram-negative infection is suspected[44]. Beta-lactams are characterized by time-dependent bactericidal activity and therefore the concentration of the (unbound) antibiotic at the site of infection must be higher than the minimum inhibitory concentration (MIC) for an adequate percentage of time in a dosing interval (%T > MIC)[45]. As sub-therapeutic dosing is associated with poorer clinical outcomes and increases the incidence of drug resistance[46–48], optimal dosing of beta-lactam antibiotics should be targeted.

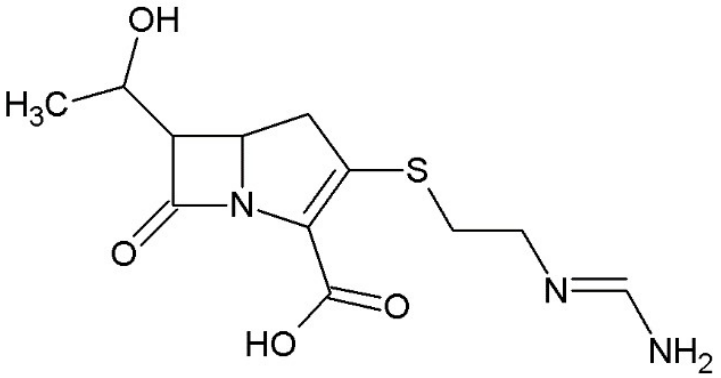
However, for critically ill patients the correct dosing of antibiotics remains a challenge and has only most recently lead to another review[49]. This is mainly due to the altered and often completely unpredictable pharmacokinetics. Furthermore, the dosing is complicated by factors related to the individual patient like a large variability in body weight and lean body mass, renal function or liver disturbances and age. Additionally, there is a lack of information on the pharmacokinetics of drugs marketed for more than a decade. Most SPC´s (summary of product characteristics) for antibiotics are completely unsatisfactory, in particular for critically ill patients.

Therefore, the aim of this chapter is to provide an overview of the results of pharmacokinetic studies of imipenem and cilastatin in critically ill patients and to compare these results with literature data of healthy volunteers.

2.1.2. Chemistry of imipenem

Imipenem is a semisynthetic thienamycin (N-formimidoyl-thienamycin) with a molecular mass of 299 g/mol. It is a weak acid with a pKa_1 of 3.2 and pKa_2 of 9.9[50]. The lipophilicity of imipenem, expressed as the logP and $logD_{pH7}$ is -2.78 ± 0.76 and -5.28, respectively[51]. The plasma protein binding of imipenem is reported to be 13 %[52].

Figure 2-1 Structural formula of imipenem.



2.1.3. Indication and dosing of imipenem

Imipenem is a parenteral broad-spectrum member of the carbapenem class of the beta-lactam antibiotics. It is used in the treatment of severe infections caused by Gram-positive and Gram-negative organisms, including beta-lactamase producing bacteria and anaerobes.

Imipenem is approved for the treatment of lower respiratory tract infections, urinary tract infections (complicated and uncomplicated), intra-abdominal infections, gynecologic infections, bacterial septicemia, bone and joint infections, skin and skin structure infections and endocarditis[53]. In contrary to meropenem, safety data for imipenem in patients with meningitis is lacking and therefore imipenem is not indicated for the treatment of meningitis.

2.1.4. Adverse events of imipenem

The most common adverse events of imipenem are gastrointestinal side effects, skin rashes, and reactions at the infusion site. A serious adverse event of imipenem is

triggering seizures, which seem to occur more frequently at high plasma concentrations of imipenem. Other carbapenems as meropenem, doripenem, ertapenem are thought to be much more less likely to cause seizures than imipenem[54]. However, the incidence of seizures with imipenem / cilastatin reported in the literature is similar to meropenem when treating severe infections in critically ill patients with CNS disorders or injuries[55].

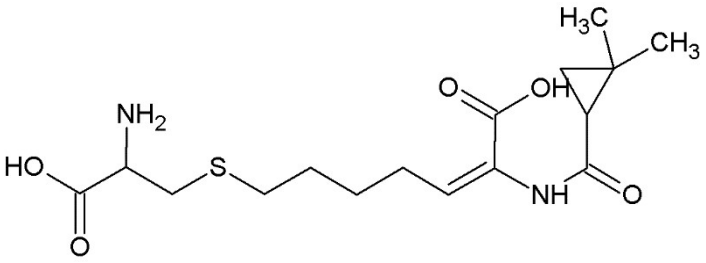
2.1.5. Co-administration of cilastatin

Imipenem is inactivated by dehydropeptidases (DHP) in the renal tubulus, resulting in low urinary concentrations of imipenem[54]. In addition, imipenem is toxic to tubular cells in high concentrations[56]. For these reasons, imipenem must be given with the DHP-1 inhibitor cilastatin (on a gram-for-gram basis), which reduces the uptake of imipenem by tubular cells and increases the clearance of imipenem in urine to 60 % – 70 %[57], making imipenem effective in the treatment of urinary tract infections.

2.1.6. Chemistry of cilastatin

The molecular mass of cilastatin is 358 g/mol. The lipophilicity of cilastatin, expressed as the logP and $logD_{pH7}$ is 2.42 ± 0.55 and -2.77. The plasma protein binding of cilastatin is reported to be 40 %[51].

Figure 2-2 Structural formula of cilastatin.



2.1.7. PK/PD - targets of imipenem

Preclinical data suggest that for the achievement of maximal bactericidal effect, the concentration of carbapenem antibiotics should exceed the MIC of the pathogen for 40 % of the dosing interval[45,58]. However, the PK/PD-target may be significantly higher under clinical conditions. Reasons for this are the clinical situation of the patient, the focus of the infection and whether further targets, such as the prevention of resistant strains of the pathogen should be achieved. Some clinicians therefore

recommend beta-lactam concentrations four to five times above the MIC, as maintaining maximum killing for the entire dosing interval could possibly shorten the duration of the infection[59]. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database Version 6.0, the PK/PD breakpoints for susceptible bacteria as pseudomonas spp. and enterococcus spp. are ≤ 4 µg/mL[60].

2.2. Methods

2.2.1. Literature search

To identify relevant articles with PK data for imipenem and cilastatin in critically ill patients, a literature search in the PubMed database was performed, using the algorithm "imipenem OR cilastatin AND (plasma OR serum) AND (concentration OR microg/mL OR mg/mL) AND (intensive care unit OR ICU OR critically ill OR sepsis OR septic shock OR ventilator associated pneumonia OR VAP)". Search filters were set to “English”, “French” or “German” language. Thereafter, a hand search was performed, in which the references of the previously obtained papers were searched for relevant articles. The resulting papers were searched for plasma levels and PK data for imipenem and / or cilastatin in critically ill patients.

A second literature search was performed to identify studies with PK data for imipenem and / or cilastatin in healthy volunteers using the algorithm "(imipenem OR cilastatin) AND pharmacokinetics AND healthy”. Search filters were set to “English”, “French” or “German” language. The resulting papers were searched for plasma levels and PK data for imipenem and / or cilastatin in healthy volunteers.

2.2.2. Data preparation and presentation

The studies were searched for information about the study population (clinical situation, number and demographical data of patients), drug administration (dosage and route of administration) and resulting PK data for imipenem and / or cilastatin. If necessary, data was converted into standardized units ($t_{1/2}$: hours, AUC: µg*h/mL, CL: L/h and Vd: L) and was extrapolated to the mean body weight of the participants of the respective study.

2.3. Results and Discussion

2.3.1. Results of the PubMed search

The PubMed search for PK data of imipenem and / or cilastatin in critically ill patients resulted in thirty-five hits and the subsequent hand search resulted in six additional papers. Twenty-five papers were excluded since these did not provide plasma or serum levels or pharmacokinetic data for imipenem and / or cilastatin in humans.

The PubMed search for PK data of imipenem and / or cilastatin in healthy volunteers resulted in forty-seven hits and the subsequent hand search resulted in two additional papers. Thirty-three papers were excluded since these did not provide plasma or serum levels or pharmacokinetic data for imipenem and / or cilastatin in healthy volunteers. One paper[52] was excluded since it included the same pharmacokinetic data as another, previously published paper[61].

2.3.2. Literature data of imipenem / cilastatin pharmacokinetics in critically ill patients

Overall, sixteen studies on the pharmacokinetics of imipenem co-administered with cilastatin in critically ill patients were included in this overview. The most recent papers were from 2014, the oldest date back to 1989. The number of patients was very limited in most studies, with a median of nine participants. However, two studies included fifty or more patients[62,63]. Cilastatin concentrations were measured in only four studies and PK data for cilastatin is therefore limited[64–67].

An overview of these studies and the resulting PK parameters for imipenem and / or cilastatin is provided in Table 2-1. The mean or median trough and peak plasma concentrations for imipenem resulting from the different studies are compared and illustrated in Figure 2-3 and 2-4.

All studies included in this overview investigated the pharmacokinetics of imipenem co-administered with cilastatin in critically ill patients. However, a number of studies focused on specific subgroups. Three studies investigated the pharmacokinetics of imipenem in critically patients with ventilator associated pneumonia (VAP)[63,68] or pneumonia[69]. Eight studies investigated the PK of imipenem in patients with severe renal dysfunction[64–67,70–73]; four of these studies determined

additionally the PK for cilastatin[64–67]. In six of these studies, patients were undergoing different types of hemodialysis[65–67,70,72,73].

The administered dose of imipenem / cilastatin differed much between and within the studies. While some patients were treated with 500 mg of imipenem co-administered with 500 mg cilastatin two times daily, others received up to 1000 mg imipenem and 1000 mg cilastatin four times daily. This difference is explained to some extend by the fact that patients with all degrees of renal function were included in the different studies. Noticeably, the renal function, together with the type or severity of infection are the only parameters used in the prescribing information for dose adjustment in adults[53]. Imipenem and cilastatin were administered intravenously as short infusion (about 30 min) in most studies. However, two studies investigated the effect of prolonged or continuous infusion on the pharmacokinetics of imipenem[68,74].

Due to the different administration settings of imipenem / cilastatin and the different clinical situations of the patients, the resulting PK parameters and plasma levels for imipenem varied significantly between the different studies (see Table 2-1). The mean terminal half-life ($t_{1/2}$) for imipenem in the different studies ranged from 1.2 hours[67] to 3.1 hours[66]. Noticeably, mean $t_{1/2}$ was over two hours in all studies on patients with acute or chronic renal failure. With the exception of the study reported by Belzberg et al.[62], all studies without the criteria of impaired renal function showed $t_{1/2}$ below or equal to two hours. A possible explanation for the long $t_{1/2}$ of 2.9 ± 1.7 hours in this study might be the large interindividual variability in creatinine clearance (104 ± 84 mL/min) of patients participating in this study, resulting in long $t_{1/2}$ for imipenem in a number of patients. As one could expect, the clearance (CL) for imipenem also showed a large variability between the different studies. The reported CL for imipenem was below 9 L/h in studies, which included patients with renal failure or severe renal dysfunction. The exception was one subgroup of patients in the study described by Fish et al.[72], which included patients receiving continuous venovenous hemodiafiltration (CVVHDF). Since CL for imipenem in this subgroup was 10.7 ± 1.1 L/h, and therefore significantly higher than in other patients receiving hemodialysis, this method seems to be very effective in the removal of imipenem from blood. The lowest CL for imipenem was found by Mueller et al.[73] with 3.9 ± 0.6 L/h in patients with chronic renal failure and the highest CL was found by Lips et al.[68] in the subgroup of patients, who were treated with prolonged infusions of imipenem / cilastatin with 18.5

± 7.8 L/h. Additionally, the volume of distribution (Vd) differed much between and within the studies and was in the range of 17.4 ± 4.0 to 47.2 ± 47.4 L[62,71]. This variability reflects the different clinical situations of the patients in the different studies as well as the large interindividual variability of this PK parameter in critically ill patients.

The number of studies, which are providing data on the exposure to imipenem, measured by the area under the curve (AUC), is very limited, as only six studies[62,65,68,71,72,75] reported this PK parameter for imipenem and only one of these studies provided additional data for cilastatin. Two studies reported the AUC per 24 hours[68,72] while the other four studies reported the AUC within one infusion interval[62,65,71,75]. Novelli et al.[71] reported an AUC within one infusion interval of 216.5 ± 86.3 µg*h/mL, which was more than twice as high as the reported AUC of the other studies. However, this value might be explained to some extend by the clinical situation of some of the included patients, who suffered from varying degrees of renal insufficiency. In addition, these patients received a relatively high dose of 1000 mg imipenem co-administered with 1000 mg cilastatin three times daily. As might be expected, the mean imipenem peak concentration (Cmax) in this study (90.10 µg/mL) was much higher than the mean Cmax values reported in all other studies (8.65 to 44.20 µg/mL, see Figure 2-4).

In addition, the trough plasma levels (Cmin) for imipenem varied widely between and within the studies, reflecting the differing interindividual PK parameters and the different study settings (see Figure 2-3). With the exception of three studies[62,74,76], all studies failed to reach mean / median trough levels of 4 µg/mL, corresponding to the MIC breakpoint for common bacteria in critically ill patients as pseudomonas spp. and enterococcus spp.[77]. However, due to the large interindividual variability, a number of patients failed to reach this PK/PD - target even in those studies.

PK parameters for cilastatin were only reported by four studies[64–67], and all of them were studying the PK for imipenem and cilastatin in patients with severely impaired renal function. However, one of these studies included additionally one subgroup with normal renal function as a comparison group[67]. The mean $t_{1/2}$ for cilastatin in these studies was in the range of 6.7 to 13.8 hours[65,67] for patients with severely impaired renal function and 0.9 hours in the comparison group of patients with normal renal function. Related to this data, the mean CL for cilastatin in these studies was only 1.7 to 1.9 L/h[65,67] for patients with impaired renal function and 12.3 L/h in the

comparison group. From these results, it can be concluded that the elimination of cilastatin is much more influenced by the renal function than the excretion of imipenem. However, the prescribing information recommends in case of impaired renal function to reduce the dosage of cilastatin to the same extend as imipenem[53]. This could potentially lead to the accumulation of cilastatin resulting in much higher exposure to cilastatin than to imipenem. Unfortunately, only one study did provide data for the exposure to imipenem and cilastatin in patients with impaired renal function. In this study, the mean ± SD AUC for imipenem was 95.3 ± 19.6 µg*h/mL and the AUC for cilastatin was 288.7 ± 76.2 µg*h/mL[65]. These results emphasize the adapted dose adjustment for the two substances. However, in addition to the fact that only a fixed combination of imipenem and cilastatin is available, there is a lack of data from clinical trials in critically ill patients with severely impaired renal function, which confirm this accumulation of cilastatin after multiple dose administration.

Table 2-1 Pharmacokinetics of imipenem / cilastatin in critically ill patients.

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage IMI/CIL [mg]	Administration route	t1/2 [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Lips et al. 2014[68]	critically ill, VAP	0.5h infusion	9	Age: 57 ± 16 years APACHE II score: 26 ± 6 Weight: 72 ± 23 kg CLCR: 85 ± 50 mL/min	1000/1000 q8h	i.v. infusion (30min)	1.8 ± 0.5	AUC_{24h}: 290.1 ± 90.7	11.4 ± 3.5	28.7 ± 9.7
		3h infusion	10	Age: 63 ± 21 years APACHE II score: 29 ± 9 Weight: 79 ± 11 kg CLCR: 101 ± 82 mL/min	500/500 q6h	i.v. infusion (3h)	1.6 ± 0.5	AUC_{24h}: 128.7 ± 53.7	18.5 ± 7.8	37.9 ± 10.9
Couffignal et al. 2014[63]	critically ill, VAP	-	51	Age: 60 years [28-84] SOFA score: 6 [2-14] Weight: 77 kg [45-126] $CLCR_{4h}$: 86 mL/min [9-571]	500/500 or 1000/1000 q8h	i.v. infusion (30min)	-	-	13.0 (RSE: 6%)	32.2 (RSE: 21%)
Afshartous et al. 2014[70]	critically ill, CVVHD	-	16 [a]	Age: - APACHE II score: - Weight: 92 ± 21 kg CLCR: -	-	i.v. infusion (30min)	-	-	7.2	33.1
Dahyot-Fizelier et al. 2010[75]	critically ill, severe peritonitis	-	8	Age: 65 ± 12 years APACHE II score: 19 ± 4 Weight: 83 ± 20 kg CLCR: 76 ± 34 mL/min	500/500 q6h	i.v. infusion (30min)	-	85.0 ± 41.2	12.0 ± 3.6	24.2 ± 6.5
Dahyot et al. 2008[78]	critically ill	-	6 [a]	Age: 53 ± 20 years SOFA score: 5 ± 2 Weight: 84 ± 21 kg CLCR: 151 ± 50 mL/min	500/500 q6h	i.v. infusion (30min)	1.4 ± 0.2	-	13.3 ± 3.3	27.2 ± 6.5

Data is presented as mean ± SD. Range is given in brackets. PK results are given for imipenem (and not for cilastatin) if not indicated otherwise.
[a] data of subgroups who were treated with other substances than imipenem or who were not critically ill is not shown; RSE: residual standard error

Table 2-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage IMI/CIL [mg]	Administration route	t1/2 [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Sakka et al. 2007[74]	critically ill	intermittent infusion	10	Age: 59 ± 16 years APACHE II score: 28 ± 5 Weight: 78 ± 14 kg CLCR: 128 ± 35 mL/min	1000/1000 q8h	i.v. infusion (40min)	-	-	12.3 ± 4.2	V_1: 12.2 ± 9.9
		continuous infusion	10	Age: 62 ± 16 years APACHE II score: 26 ± 6 Weight: 73 ± 8 kg CLCR: 122 ± 33 mL/min	2000/2000 /24h	i.v. infusion (continuous infusion)	-	-		
Novelli et al. 2005[71]	critically ill	-	10	Age: 65 ± 19 years APACHE II score: - Weight: 75 ± 12 kg CLCR: 76 ± 34 mL/min	1000/1000 q8h	i.v. infusion (30min)	2.0 ± 0.3	216.5 ± 86.3	7.0 ± 2.5	17.7 ± 4.0
Fish et al. 2005[72]	critically ill	CVVH	6	Age: 50 ± 17 years APACHE II score: 29 ± 4 Weight: 94 ± 15 kg CLCR: -	500/500 q8h or q12h	i.v. infusion (30min)	2.7 ± 1.3	AUC24h: 147.4 ± 35.8	8.7 ± 1.1	33.8 ± 9.4 /94kg
		CVVHDF	6				2.6 ± 1.6	AUC24h: 125.4 ± 24.3	10.7 ± 1.1	34.8 ± 12.2 /94kg
Belzberg et al. 2004[62]	critically ill	-	50	Age: 45 ± 17 years APACHE II score: 20 ± 8 Weight: 80 ± 18 kg CLCR: 104 ± 84 mL/min	500/500 or 1000/1000 q6h	i.v. infusion (30min)	2.9 ± 1.7	79.1 ± 62.3	12.1 ± 12.0	47.2 ± 47.4
Tegeder et al. 2002[76]	critically ill	-	6 [a]	Age: 64 ± 17 years APACHE II score: - Weight: 84 ± 19 kg SCr: 2.2 ± 0.9 mg/dL	500/500 q6h or q8h	i.v. infusion (20min)	-	-	6.3 ± 0.8	18.5 ± 4.4

Data is presented as mean ± SD. PK results are given for imipenem (and not for cilastatin) if not indicated otherwise.
[a] data of subgroups who were treated with other substances than imipenem or who were not critically ill is not shown; V_1: volume of distribution in the central compartment

Table 2-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage IMI/CIL [mg]	Administration route	t1/2 [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Tegeder et al. 1997[64]	critically ill, acute renal failure	-	12	Age: 66 ±s APACHE II score: - Weight: - CLCR: -	500/500 q6h or q8h	i.v. infusion (about 30-60min)	2.9 ± 1.4	-	7.3 ± 1.7	24.3 ± 7.7
							CIL: 9.7 ± 4.4	-	CIL: 1.8 ± 0.8	CIL: 19.6 ± 7.3
Hashimoto et al. 1997[65]	critically ill, CVVHD	-	6	Age: 54 years [15-68] APACHE II score: - Weight: 54 kg SCr: 5.5 ± 1.0 mg/dL	500/500 q12h	i.v. infusion (30min)	2.8 ± 0.7	95.3 ± 19.6	5.4 ± 1.1	19.3 ± 6.0
							CIL: 6.7 ± 0.9	CIL: 288.7 ± 76.2	CIL: 1.90 ± 0.5	CIL: 12.5 ± 2.4
McKindley et al. 1996[69]	critically ill, pneumonia	-	10	Age: 44 ± 12 years APACHE II score: - Weight: 90 ± 27 kg CLCR: 85 ± 17 mL/min/m2	500/500 q6h	i.v. infusion (30min)	1.6 ± 1.3	-	14.4 ± 4.5 /90kg	31.5 ± 11.7 /90kg
Kihara et al. 1994[66]	critically ill, slow hemo-dialysis	-	7	Age: 71 ± 11 years APACHE II score: - Weight: 48 kg SCr: 8.7 ± 1.8 mg/dL	500/500 (single dose)	i.v. infusion (30min)	3.1 ± 0.3	-	5.0 ± 0.4	18.8 ± 2.2
							CIL: 9.7 ± 1.2	-	CIL: 1.9 ± 0.1	CIL: 13.8 ± 1.3
Mueller et al. 1993[73]	critically ill, renal failure	acute renal failure	7	Age: 50 ± 20 years APACHE II score: - Weight: 85 ± 20 kg CLCR: -	500/500 q6h or q8h	i.v. infusion (30min)	2.9 ± 1.0	-	6.5 ± 0.8	27.1 ± 6.8
		chronic renal failure	3	Age: 74 ± 9 years APACHE II score: - Weight: 70 ± 1 kg CLCR: -			3.0 ± 0.8	-	3.9 ± 0.6	19.1 ± 4.6

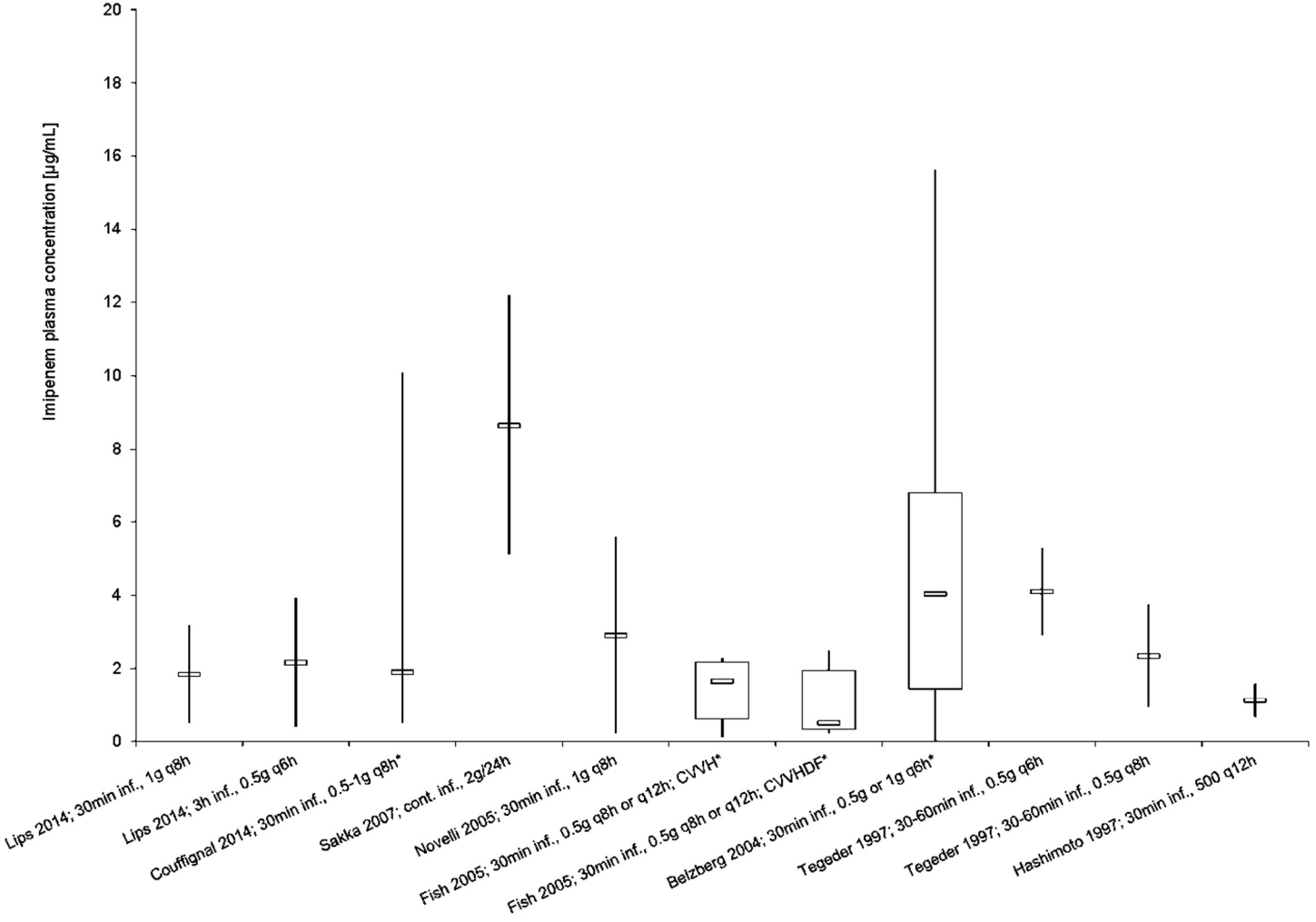
Data is presented as mean ± SD. Range is given in brackets. PK results are given for imipenem (and not for cilastatin) if not indicated otherwise.
CIL: PK results for cilastatin

Table 2-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage IMI/CIL [mg]	Administration route	t1/2 [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Keller et al. 1989[67]	critically ill	CAVH	8	Age: 60 ± 11 years APACHE II score: - Weight: 71 ± 11 kg SCr: 4.1 ± 1.6 mg/dL	500/500 (single dose)	i.v. infusion (15min)	2.2 ± 0.1	-	6.2 ± 0.7	19.4 ± 2.0
							CIL: 13.8 ± 4.5		CIL: 1.7 ± 0.6	CIL: 18.3 ± 4.3
		without renal failure	2	Age: 22 ± 9 years APACHE II score: - Weight: 68 ± 0 kg SCr: 1.0 ± 0.1 mg/dL			1.2 ± 0.4	-	17.0 ± 13.6	25 ± 5
							CIL: 0.9 ± 0.4		CIL: 12.3 ± 10.1	CIL: 21.3 ± 2.5

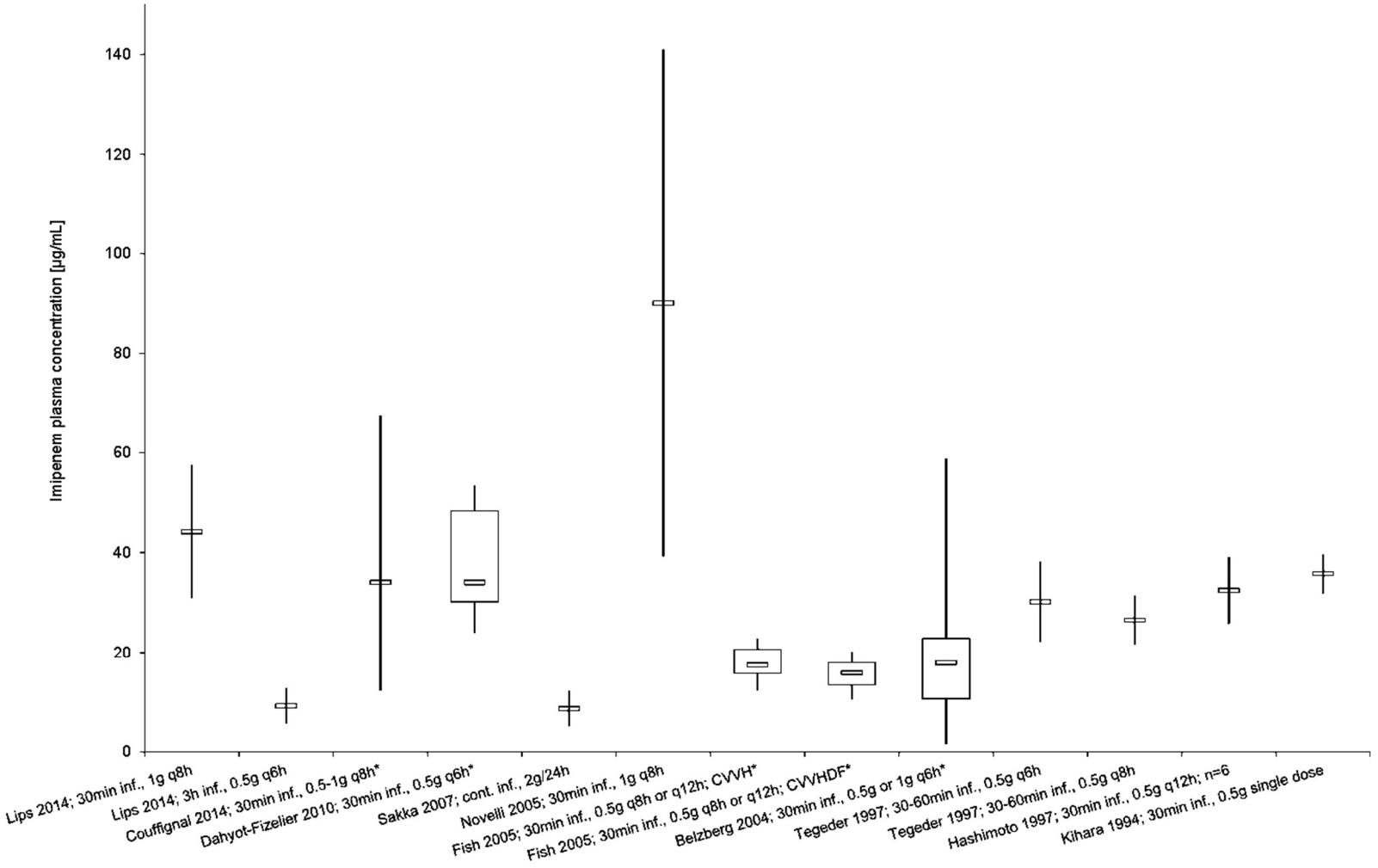
Data is presented as mean ± SD. PK results are given for imipenem (and not for cilastatin) if not indicated otherwise.
CIL: PK results for cilastatin

Figure 2-3 Literature data of imipenem trough plasma / serum levels (Cmin) in critically ill patients.



If not indicated otherwise, data is shown as the mean ± SD.
* Data is presented as the median (dash), the minimum and maximum range (whisker) and with or without the IQR (box).

Figure 2-4 Literature data of imipenem peak plasma / serum levels (Cmax) in critically ill patients.



If not indicated otherwise, data is shown as the mean ± SD.
* Data is presented as the median (dash), the minimum and maximum range (whisker) and with or without the IQR (box).

2.3.3. Literature data of imipenem / cilastatin pharmacokinetics in healthy volunteers

Fourteen studies on the pharmacokinetics of imipenem co-administered with cilastatin and one study without the co-administration of cilastatin in healthy volunteers were included in this overview. The most recent paper was from 2010, the oldest date back to 1983. The number of participants was in the range of four to eighteen.

An overview of these studies and the resulting PK parameters is provided in Table 2-2. The trough and peak plasma concentrations for imipenem resulting from the different studies are compared and illustrated in Figure 2-5 and 2-6.

All studies included in this overview investigated the PK of imipenem with or without cilastatin in healthy volunteers. However, a number of studies focused on factors influencing the PK of imipenem and cilastatin. Lee et al.[79] and Jaruratanasirikul et al.[80] studied the influence of prolonged infusions and Adamis et al.[81] and Norrby et al.[82] studied the influence of the co-administration of amikacin and probenecid on imipenem PK. In contrast to the other studies, which included healthy volunteers of younger age, Toon et al.[83] studied imipenem and cilastatin PK in elderly healthy volunteers. In addition, this was the only study in healthy volunteers, which investigated multiple dose PK of imipenem. The dosage of imipenem in the different studies was either 250, 500 or 1000 mg co-administered with an equal dose of cilastatin. However, in two studies described by Norrby et al.[82,84] imipenem was administered without cilastatin or with a different dose of cilastatin in some subgroups.

The reported mean ± SD $t_{1/2}$ for imipenem was in the range of 0.8 to 1.3 hours except of two studies, which reported a much longer $t_{1/2}$. One of these[80] reported a mean ± SD $t_{1/2}$ of 2.4 ± 0.3 hours in patients receiving a prolonged infusion of 1000 mg imipenem. The second one[81] reported mean ± SD imipenem $t_{1/2}$ of 5.0 ± 2.0 and 3.5 ± 2.9 hours, respectively, in patients who were treated with 500 mg imipenem without and with co-administration of amikacin. However, the reported imipenem CL in this study was also much higher than the imipenem CL reported by others. While other studies reported a mean imipenem CL in the range of 8.0 to 14.5 L/h[78,80], Adamis et al.[81] reported a mean imipenem CL of 30.6 and 25.2 L/h without and with co-administration of amikacin. If these values were used for the calculation of Vd for imipenem, this would result in highly improbable values of 220 and 127 L, respectively. However, the Vd for imipenem was not reported in this study. The mean Vd for

imipenem reported by other authors was in the range of 9.4[80] to 22.8[85]. However, a number of studies used compartmental analysis for the determination of the PK parameters for imipenem and provided only values of the volume of distribution in the central compartment (V_1). The results of these studies were in the range of 7.4[79] to 11.5 L[84].

As one could expect, Cmax and AUC for imipenem in healthy individuals were mainly dependent on the administered dose, the duration of the infusion and the route of administration. Mean Cmax after the administration of 1000 mg imipenem over 30 minutes was in the range of 58.9[52] to 69.9[86] µg/mL and the administration of the same dose as prolonged infusion over two hours resulted in a mean Cmax of 43.91 µg/mL[80]. When excluding the study of Adamis et al. from this analysis - due to the reasons described above - the mean or median plasma / serum concentrations after intravenously administration of 500 mg imipenem were in the range of 19.3[85] to 48.4[80] µg/mL. In one subgroup of the study by Signs et al.[85], imipenem was administered intramuscularly, leading to a mean Cmax of only 8.0 µg/mL. The resulting mean AUC of the two studies, in which patients received 250 mg of imipenem was 18.7 and 22.2 µg*h/mL[82,84], respectively. However, in one of these studies imipenem was administered without cilastatin[82]. The administration of 500 mg of imipenem, co-administered with an equal dose of cilastatin, resulted in a mean AUC of 22.1 to 63.7 µg*h/mL[80,85], and the mean AUC after administration of 1000 mg of imipenem was in the range of 63.9 to 127.1 µg*h/mL[80,85].

PK parameters in healthy volunteers for cilastatin were only reported by two studies[83,84]. As noted above, Toon et al. studied imipenem / cilastatin single and multiple dose PK in elderly healthy volunteers[83] and Norrby et al. studied imipenem / cilastatin PK for different doses of imipenem and cilastatin[60]. The mean $t_{1/2}$ and CL for cilastatin in elderly healthy volunteers was 1.3 ± 0.4 and 7.7 ± 2.3 L/h, respectively, for single dose administration and 1.2 ± 0.3 h and 7.2 ± 2.0 L/h, respectively, for multiple dose administration[83]. The reported $t_{1/2}$ for cilastatin in young (30 to 31 years) healthy volunteers was 0.8 ± 0.1 h and therefore significantly shorter and independent of dose (250 or 500 mg); CL was not reported in this study[84]. As one could expect, the AUC in elderly healthy volunteers was significantly higher than in young healthy volunteers. AUC in elderly healthy volunteers after the administration of 500 mg cilastatin was 72.2 ± 25.0 and 76.4 ± 21.6 µg*h/mL after single and multiple dose, respectively[83], while

AUC in young healthy volunteers was 40.0 ± 6.3 µg*h/mL[84]. Mean Vd in elderly healthy volunteers was reported to be 13.0 ± 2.0 and 12.4 ± 3.3 L after single or multiple dose, respectively[83]. The reported mean Vd in young healthy volunteers was in the range of 7.5 to 8.4 L[84] and therefore significantly lower than in the study on elderly healthy individuals.

Table 2-2 Pharmacokinetics of imipenem / cilastatin in healthy volunteers.

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Subject demographics	Dosage IMI/CIL [mg]	Administration route	t1/2 [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Lee et al. 2010[79]	healthy volunteers	0.5h infusion	18 [b]	Age: 38 ± 10 years Weight: 74 ± 9 kg CLCR: -	1000/1000 (single dose)	i.v. infusion (30min)	-	82.7 ± 24.0	12.1 ± 3.5	V_1: 9.7 ± 5.5
		3h infusion				i.v. infusion (3h)	-	84.6 ± 17.7	11.8 ± 2.5	V_1: 7.4 ± 2.6
Dahyot et al. 2008[78]	healthy volunteers	-	6 [a]	Age: 25 ± 3 years Weight: 71 ± 15 kg CLCR: -	500/500 (single dose)	i.v. infusion (30min)	1.0 ± 0.1	-	14.5 ± 3.2	21.0 ± 5.0
Jaruratanasirikul et al. 2005[80]	healthy volunteers	0.5h infusion	8 [a]	Age: 25 ± 3 years Weight: 71 ± 15 kg CLCR: -	500/500 (single dose)	i.v. infusion (30min)	1.3 ± 0.3	63.7 ± 7.4	8.0 ± 1.0	9.4 ± 1.4
		2h infusion			500/500 (single dose)	i.v. infusion (2h)	1.0 ± 0.2	59.0 ± 6.8	8.6 ± 1.1	9.4 ± 1.8
		2h infusion			1000/1000 (single dose)	i.v. infusion (2h)	2.4 ± 0.3	127.1 ± 17.3	8.0 ± 1.1	11.6 ± 2.0
Adamis et al. 2004[81]	healthy volunteers	imipenem without amikacin	6 [b]	Age: 29 ± 9 years Weight: - SCr: 0.8 ± 0.1 mg/dL	500/500 (single dose)	i.v. infusion (30min)	5.0 ± 2.0	27.7 ± 22.5	30.6 ± 21.23	-
		imipenem with 0.5g amikacin					3.5 ± 2.9	24.8 ± 11.7	25.2 ± 12.4	-
Tegeder et al. 2002[76]	healthy volunteers	-	5 [a]	Age: [25-31] years Weight: normal CLCR: -	500/500 (single dose)	i.v. infusion (20min)	-	-	13.3 ± 1.4	13.9 ± 2.5

Data is presented as mean ± SD. PK results are given for imipenem (and not for cilastatin) if not indicated otherwise.
[a] data of subgroups who were treated with other substances than imipenem or who were not critically ill is not shown; [b] crossover study design; V_1: volume of distribution in the central compartment

Table 2-2 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Subject demographics	Dosage IMI/CIL [mg]	Administration route	t1/2 [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Dreetz et al. 1996[87]	healthy volunteers	-	12	Age: 29 ± 6 years Weight: 80 ± 7 kg CLCR: 112 ± 13 mL/min/1.73m^2	1000/1000 (single dose)	i.v. infusion (30min)	1.1 ± 0.2	96.1 ± 14.4	10.5 ± 1.4 /1.73m^2	15.3 ± 3.3 /70kg
Paradis et al. 1992[88]	healthy volunteers	-	15	Age: 24 years [20-35] Weight: 72 kg [64-83] CLCR: -	500/500 (single dose)	i.v. infusion (30min)	1.1 ± 0.5	37.6 ± 6.3	12.8 ± 1.0 /72kg	15.5 ± 1.5
Signs et al. 1992[85]	healthy volunteers	0.5g i.v.	4	Age: 21-48 years Weight: - CLCR: -	500/500 (single dose)	i.v. infusion (30min)	0.9 ± 0.0	22.1 ± 5.5	-	22.8 ± 5.9
		1g i.v.	10		1000/1000 (single dose)		1.0 ± 0.1	63.9 ± 9.1	-	21.2 ± 2.9
		0.5g i.m.	8		500/500 (single dose)	i.m.	1.3 ± 0.4	27.8 ± 6.7	-	14.3 ± 12.2
Nilsson-Ehle et al. 1991[86]	healthy volunteers	-	8	Age: 33 years [22-38] Weight: 74 kg [66-86] CLCR: -	1000/1000 (single dose)	i.v. infusion (30min)	1.1	94.4 ± 12.0	11.0 ± 1.5	14.4 ± 1.2
Toon et al. 1987[83]	healthy elderly volunteers	single dose	6	Age: 70 years [66-75] Weight: 65 kg [54-77] CLCR: -	500/500 (single dose)	i.v. infusion (20min)	1.0 ± 0.2	46.1 ± 7.9	11.4 ± 2.6	15.6 ± 2.6 /65kg
							CIL: 1.3 ± 0.4	CIL: 72.2 ± 25.0	CIL: 7.7 ± 2.3	CIL: 13.0 ± 2.0 /65kg
		multiple dose			500/500 q6h		1.1 ± 0.2	49.1 ± 5.4	10.5 ± 1.8	15.6 ± 2.0 /65kg
							CIL: 1.2 ± 0.3	CIL: 76.4 ± 21.6	CIL: 7.2 ± 2.0	CIL: 12.4 ± 3.3 /65kg

Data is presented as mean ± SD. Range is given in brackets. PK results are given for imipenem (and not for cilastatin) if not indicated otherwise.
CIL: PK results for cilastatin

Table 2-2 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Subject demographics	Dosage IMI/CIL [mg]	Administration route	t1/2 [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Drusano et al. 1984[61]	healthy volunteers	-	6	Age: [18-35] years Weight: [61-84] kg CLCR:	1000/1000 IMI/CIL (single dose)	i.v. infusion (30min)	1.3 ± 0.4	85.7 ± 3.8	10.1 ± 1.0 /1.73m^2	16.6 ± 2.2
Norrby et al. 1984[84]	healthy volunteers	500/0 IMI/CIL	4 [b]	Age: [30-31] years Weight: [71-87] kg CLCR: -	500/0 (single dose)	i.v. infusion (20min)	0.8 ± 0.2	34.5 ± 8.4	-	V_1: 11.5 ± 3.2
							-	-	-	-
		500/500 IMI/CIL			500/500 (single dose)		0.8 ± 0.1	38.9 ± 9.5	-	V_1: 10.9 ± 2.6
							CIL: 0.8 ± 0.1	CIL: 40.0 ± 6.3	-	CIL: V_1: 9.6 ± 0.8
		0/250 IMI/CIL			0/250 (single dose)		-	-	-	-
							CIL: 0.8 ± 0.1	CIL: 21.3 ± 3.1	-	CIL: V_1: 8.4 ± 1.0
		250/250 IMI/CIL			250/250 (single dose)		0.8 ± 0.1	22.2 ± 1.9	-	V_1: 11.3 ± 1.0
							CIL: 0.8 ± 0.1	CIL: 22.1 ± 1.9	-	CIL: V_1: 8.3 ± 1.3
		1000/250 IMI/CIL			1000/250 (single dose)		0.6 ± 0.1	77.7 ± 16.2	-	V_1: 11.3 ± 1.9
							CIL: 0.8 ± 0.1	CIL: 23.7 ± 2.5	-	CIL: V_1: 7.5 ± 1.1
Norrby et al. 1983[89]	healthy volunteers	500/500 IMI/CIL	8	Age: 25 years [18-40] Weight: 75 kg [60-89] CLCR: -	500/500 (single dose)	i.v. infusion (20min)	1.0 ± 0.1	43.2 ± 4.7	11.7 ± 1.4	V_1: 10.4 ± 1.7
		1000/1000 IMI/CIL	8		1000/1000 (single dose)		1.0 ± 0.1	91.6 ± 12.8	11.2 ± 0.1	V_1: 9.9 ± 1.0

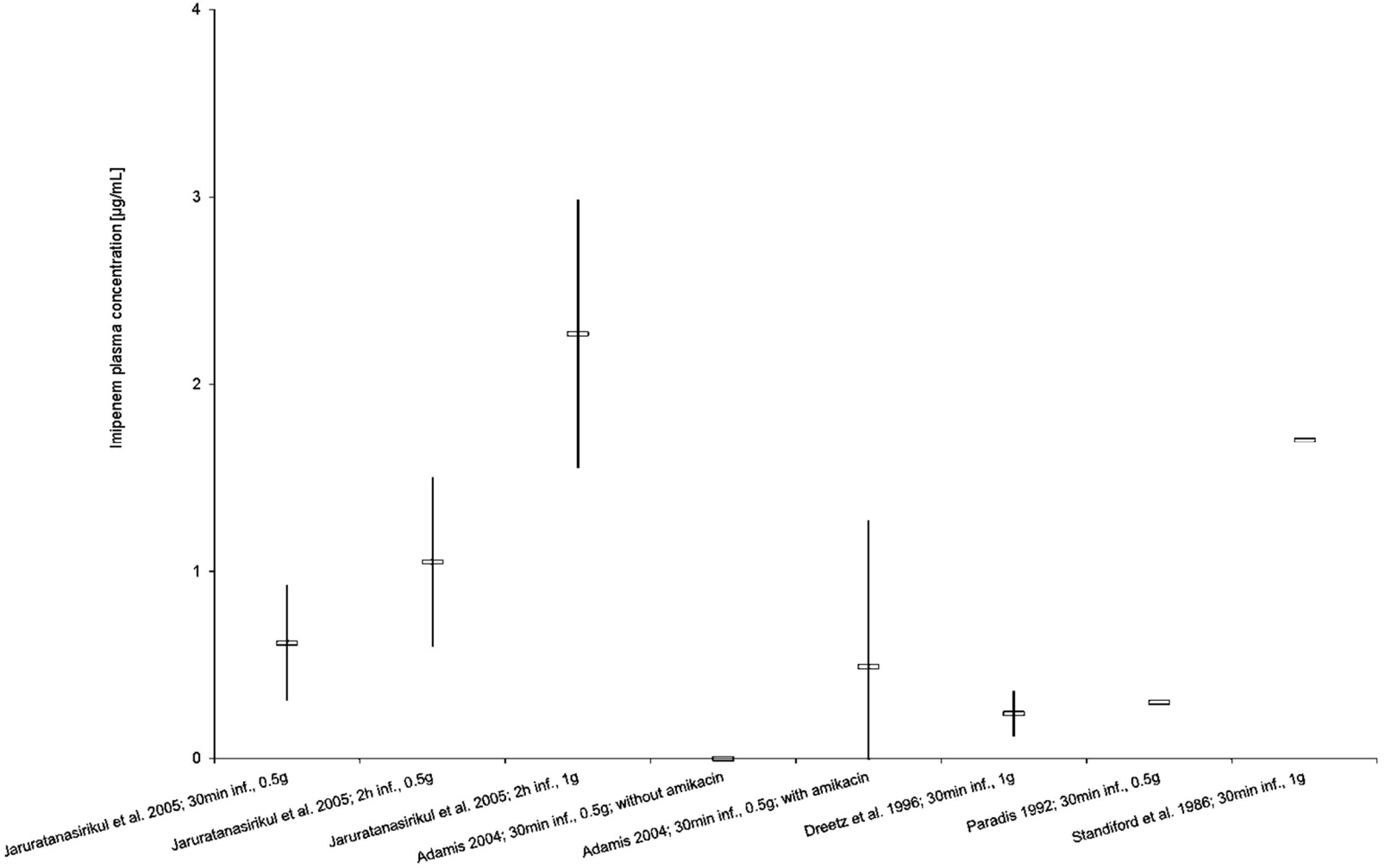
Data is presented as mean ± SD. Range is given in brackets. PK results are given for imipenem (and not for cilastatin) if not indicated otherwise.
[a] data of subgroups who were treated with other substances than imipenem or who were not critically ill is not shown; [b] crossover study design; V_1: volume of distribution in the central compartment CIL: PK results for cilastatin

Table 2-2 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Subject demographics	Dosage IMI/CIL [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Norrby et al. 1983[90]	healthy volunteers	500/500 IMI/CIL	8	Age: 25 years [19-38] Weight: 75 kg [60-89] CLCR: -	500/500 (single dose)	i.v. infusion (20min)	1.0 ± 0.1	37.3 ± 3.8	10.5 ± 0.6 /1.73m^2	-
		1000/1000 IMI/CIL	8		1000/1000 (single dose)		1.0 ± 0.1	81.9 ± 13.5	10.1 ± 1.1 /1.73m^2	-
Norrby et al. 1983[82]	healthy volunteers	imipenem without probenecid	12 [b]	Age: 25 years [19-38] Weight: 75 kg [60-89] CLCR: -	250 IMI (single dose)	i.v. infusion (5min)	0.9 ± 0.1	18.7 ± 2.2	12.6 ± 1.3 /1.73m^2	V_1: 10.6 ± 2.3
		imipenem with probenecid					1.0 ± 0.0	21.1 ± 2.3	11.2 ± 1.0 /1.73m^2	V_1: 9.9 ± 2.2

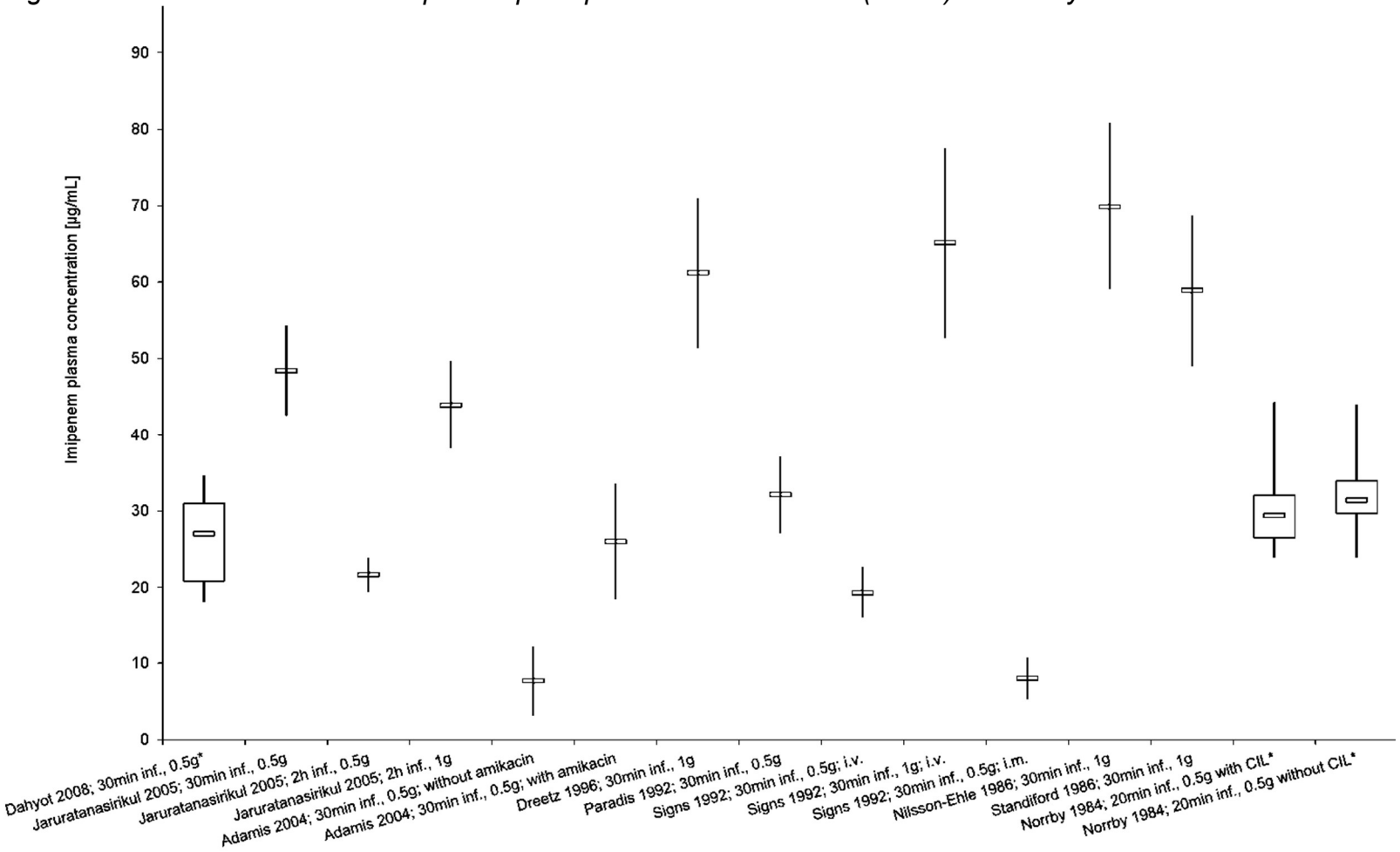
Data is presented as mean ± SD. Range is given in brackets. PK results are given for imipenem (and not for cilastatin) if not indicated otherwise.
[b] crossover study design; V_1: volume of distribution in the central compartment

Figure 2-5 Literature data of imipenem minimum plasma / serum levels (Cmin) in healthy volunteers.



Imipenem / cilastatin was administered as single dose. Data is shown as the mean ± SD.

Figure 2-6 Literature data of imipenem peak plasma / serum levels (Cmax) in healthy volunteers.

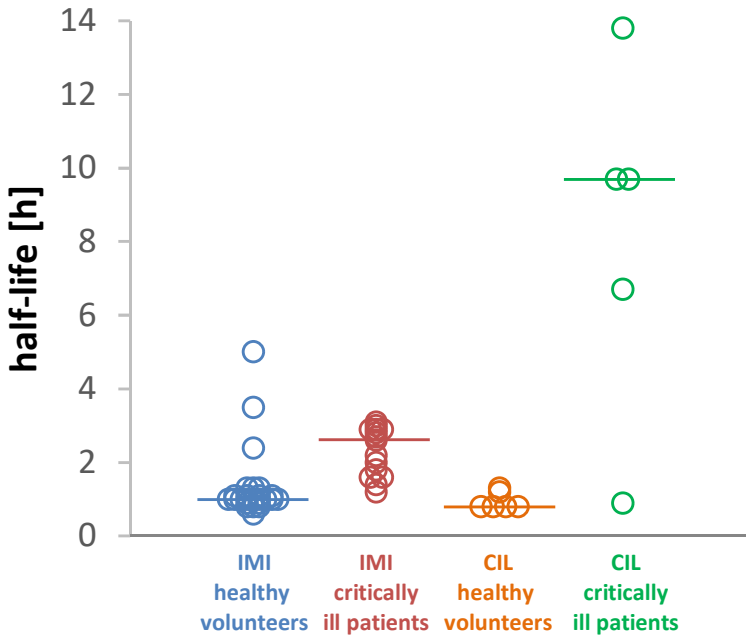


If not indicated otherwise, imipenem / cilastatin was administered as single dose and data is shown as the mean ± SD.
* Data is presented as the median (dash), the minimum and maximum range (whisker) and with or without the IQR (box).

2.3.4. Differences in the pharmacokinetics of imipenem / cilastatin in critically ill patients and healthy volunteers

As shown in Figure 2-7, the median $t_{1/2}$ for imipenem in studies on healthy volunteers was significantly below the median $t_{1/2}$ resulting from studies in critically ill patients (1.0 vs. 2.6 h). However, due to the wide variability of this PK parameter in critically ill patients, a number of these patients might show equal or even shorter $t_{1/2}$ for imipenem than healthy volunteers. This difference between healthy individuals and critically ill patients is even more remarkably for the $t_{1/2}$ of cilastatin (0.8 vs. 9.7 h). However, all studies reporting the $t_{1/2}$ for cilastatin in critically ill patients were focused on patients with severely impaired renal function, with the exception of one subgroup of the study by Keller et al.[67], which included critically ill patients with normal renal function. The fact that the $t_{1/2}$ in this subgroup was in the same range as the $t_{1/2}$ in healthy individuals emphasizes the importance of the renal function on the elimination of cilastatin.

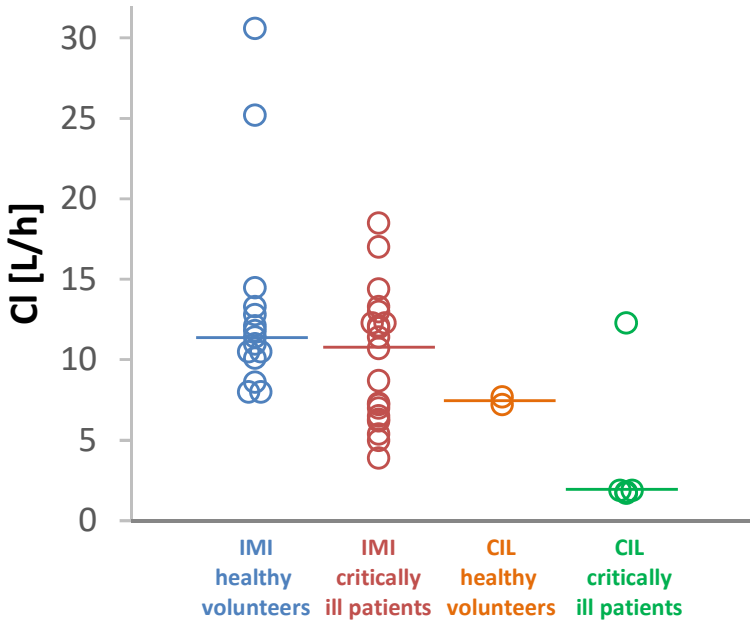
Figure 2-7 Half-life of imipenem and cilastatin in healthy volunteers and critically ill patients.



The lines indicate the medians of all studies in one group, and each circle indicates the mean half-life of one study or one study-subgroup.

The median CL for imipenem in critically ill patients was approximately as high as the CL for imipenem in healthy subjects (10.7 vs. 11.4 L/h), as shown in Figure 2-8. However, the reported imipenem CL varied much more between the different studies in critically ill patients than between the different studies in healthy volunteers. The extremely high imipenem CL co-administered without and with amikacin of 30.6 and 25.2 L/h in healthy volunteers reported by Adamis et al.[81] is inexplicable. The number of studies which reported cilastatin CL in healthy volunteers is very limited and could therefore hardly be compared with the results in critically ill patients. Additionally, studies reporting this PK parameter in critically ill patients included only patients with severely impaired renal function (with the exception of one comparison group). The resulting mean cilastatin CL of the two studies in healthy volunteers was 7.45 L/h and the resulting median cilastatin CL in critically ill patients was 1.9 L/h.

Figure 2-8 Clearance of imipenem and cilastatin in healthy volunteers and critically ill patients.

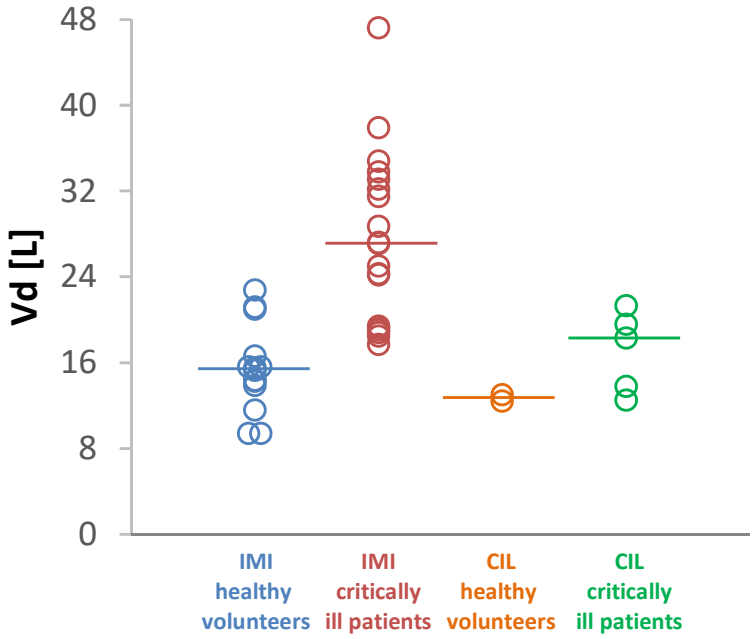


The lines indicate the medians of one group, and each circle indicates the mean clearance of one study or one study subgroup.

The Vd for both substances varied significantly between healthy volunteers and critically ill patients, as can be seen in Figure 2-9. While the median Vd of imipenem was 15.4 L in studies on healthy volunteers, the resulting median Vd in critically ill

patients was almost twice as high (27.1 L). The same applies to the Vd of cilastatin, which was in median 12.7 L in healthy volunteers and 18.3 L in critically ill patients.

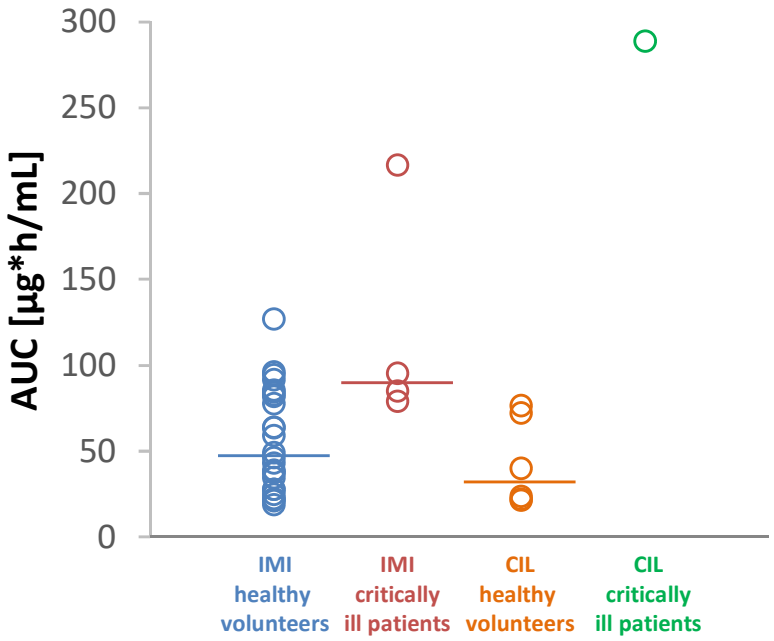
Figure 2-9 Volume of distribution of imipenem and cilastatin in healthy volunteers and critically ill patients.



The lines indicate the medians of one group, and each circle indicates the mean volume of distribution of one study or one study subgroup.

Few studies reported the AUC for imipenem and cilastatin in critically ill patients. Resulting from these few studies, the median AUC for imipenem in critically ill patients was almost twice as high as the median AUC in healthy volunteers (47.6 vs. 90.2 µg*h/mL). However, this result is not astonishing, as critically ill patients received most often higher dosages and were dosed several times, while healthy volunteers received only single-dose treatment. In addition, resulting from the data of $t_{1/2}$ and CL for imipenem in critically ill patents, the elimination of imipenem is significantly limited in a number of critically ill patients. Only one study provided the resulting AUC for cilastatin in critically ill patients. However, while the AUC for cilastatin in healthy volunteers was in the same order of magnitude as the AUC for imipenem in healthy volunteers (31.9 vs. 47.6 µg*h/mL), the AUC for cilastatin in critically ill patients was several times higher than the median AUC for imipenem in critically ill patients (288.7 vs. 90.2 µg*h/mL).

Figure 2-10 Area under the curve of imipenem and cilastatin in healthy volunteers and critically ill patients.



The lines indicate the medians of one group, and each circle indicates the mean area under the curve of one study or one study subgroup.

2.4. Conclusion

This retrospective data analysis provides an overview of the existing PK data of imipenem and cilastatin in critically ill patients and healthy volunteers. As pointed out, the PK of imipenem and cilastatin in critically ill patients varied substantially between and within the studies compared with healthy individuals. Additionally, clinical factors like renal function seem to have a different influence on the PK of imipenem and cilastatin, suggesting that a fixed combination of these substances might be disadvantageous for this vulnerable group of patients. As achieving and maintaining adequate plasma levels of antibiotics is highly important to the clinical course and survival of critically ill patients, these results emphasize the importance of monitoring the blood levels of imipenem and cilastatin in critically ill patients.

3. Accumulation of cilastatin but not of imipenem in intensive care unit patients with sepsis: individualizing prolonged infusions by population pharmacokinetics

3.1. Introduction

Imipenem is a broad-spectrum beta-lactam antibiotic that is commonly used for empiric therapy of critically ill patients[91]. As imipenem is inactivated by dehydropeptidase enzymes (DHP) in the renal tubulus, imipenem is co-administered with the DHP-1 inhibitor cilastatin[92]. Clearance and the volume of distribution and consequently the concentrations of antibiotics are highly variable in critically ill patients. For fixed dose combinations such as imipenem / cilastatin, it is important to account for the potentially different fraction of drug excreted unchanged in urine. Renal function changes will have a substantial impact on drugs that are predominantly renally cleared, whereas the impact is less for drugs with a substantial nonrenal clearance component. A few prior studies in critically ill patients who underwent dialysis suggested that cilastatin reaches higher than expected plasma concentrations[64–67]. However, these studies only had small sample sizes (i.e. 12 patients or fewer), were not analyzed by population pharmacokinetics, and have not led to changes in the current dosing recommendations for critically ill patients.

According to the prescribing information[93], the dosage of imipenem and cilastatin is adjusted based on creatinine clearance, body weight, as well as the localization and severity of infection. Dose adjustment based on these criteria does not adequately capture patients who are critically ill[62]. Therefore, dosing of critically ill patients with unstable pharmacokinetics is most commonly performed empirically in clinical practice, as imipenem and cilastatin concentrations are not routinely measured to individualize doses via therapeutic drug management (TDM)[94,95].

The first objective of this study was to characterize the pharmacokinetics of imipenem and cilastatin in intensive care unit (ICU) patients. Our second objective was to implement a clinically feasible TDM program for imipenem and cilastatin. The third objective was to identify potential pharmacokinetic risk factors, which may lead to accumulation of cilastatin concentrations during therapy.

An additional objective was to compare the results of a sophisticated population pharmacokinetic analysis of the imipenem / cilastatin data with a simple non-compartmental approach.

3.2. Methods

3.2.1. Study design and population

This prospective cohort study was carried out in the surgical intensive care unit of the Paracelsus Medical University, Nürnberg, Germany, from January to October 2014. Eligibility criteria were age ≥18 years and the diagnosis of abdominal infection (peritonitis, organ infection) or pneumonia. This study included patients with or without sepsis, severe sepsis or septic shock who were treated with imipenem / cilastatin. Exclusion criteria were severe anemia or known allergy to imipenem or cilastatin. The study was approved by the local Ethics Committee and is registered in the United States National Library of Medicine (no. NCT01702545) and the German Register of Clinical Trials („Deutsches Register Klinischer Studien“; no. DRKS00004392).

3.2.2. Data collection

Patient demographics and clinical data were collected at the first day of imipenem treatment. Serial measurements of serum creatinine (daily) were performed before, during and after the initiation of antimicrobial therapy.

3.2.3. Imipenem / cilastatin administration and sample collection

Imipenem / cilastatin doses of 500 mg / 500 mg or 1000 mg / 1000 mg two or three times daily were used for empiric therapy before measured concentrations from TDM became available. Doses were selected by the attending clinician. All patients received a loading dose of 1000 mg / 1000 mg imipenem / cilastatin as short-term infusion. The second and subsequent doses were given as 3-h infusions via an infusion pump through a central venous catheter. The infusion line was rinsed with saline at the same rate as the imipenem / cilastatin infusion to assure complete dosing of imipenem / cilastatin.

Blood samples (2 mL) were drawn from an arterial line at the end of infusion (“peak”), as well as two hours before and immediately before (“trough concentration”) the next infusion. Blood samples were collected in K_3-EDTA tubes and immediately

cooled in an ice water bath for at least 5 min. Within 15 min, samples were centrifuged for 5 min at 1500 *g* and +4 °C. A volume of 100 µl of the resulting plasma was added to 100 µl of stabilizer solution (morpholinopropanesulfonic acid buffer, 1.0 M, pH 7.0). The resulting mixture was intensively agitated for at least 15 seconds by an automatic shaker and then immediately frozen on dry ice and stored at -80 °C until analysis.

3.2.4. Quantification of imipenem / cilastatin concentrations

Imipenem and cilastatin concentrations were quantified using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay developed at the IBMP by Christoph Stelzer and Martina Kinzig. Analysis of independently prepared quality control samples for imipenem and cilastatin indicated good reproducibility as the resulting coefficient of variation was in the range of 5.3 to 7.5% for imipenem and 6.1 to 7.2% for cilastatin. The accuracy of these quality control samples was in the range of 93.8 to 98.2% for imipenem and 95.4 to 98.1% for cilastatin (measured concentrations vs. target concentrations). The limit of quantification was 0.5 mg/L for both imipenem and cilastatin.

For imipenem, the liquid chromatography systems consisted of a binary LC-pump (Agilent 1200 Series, Agilent Technologies, Waldbronn, Germany) and an analytical column (Nucleosil 100 NH_2, 5 µm, 40 x 4.6 mm, Alltech Grom GmbH, Rottenburg, Germany). Isocratic elution was performed with 0.01 M ammonium acetate buffer (65 %) and acetonitrile (35 %). Determination was performed using an AB SCIEX API 5000 triple quadrupole mass spectrometer (AB SCIEX, Concord, Ontario, Canada) and Analyst software version 1.6.2 (AB SCIEX, Concord, Ontario, Canada). In brief, 100 µL of each sample was placed in a polypropylene-tube. Samples were deproteinized with 200 µL acetonitrile (containing the internal standard meropenem), subsequently vortex-shaked and centrifuged. The supernatant was further diluted with 0.01 M ammonium acetate buffer and 20 µL of each samples were injected into the LC-MS/MS system. The samples for imipenem were detected with MRM (Multiple Reaction Monitoring) as follows: precursor → product ion for imipenem 100.20 → 97.90 m/z and for meropenem (internal standard) 384.00 → 114.10 m/z; for all analytes in positive mode. Under these conditions imipenem eluted after 0.9 minutes and the internal standard after 1.2 minutes.

For cilastatin, the liquid chromatography systems consisted of a binary LC-pump (Agilent 1200 Series, Agilent Technologies, Waldbronn, Germany) and an analytical column (Kinetex 2.6 u C18, 100 A, 50 x 4.6 mm, Phenomenex, Aschaffenburg, Germany). Gradient elution was performed with 0.1% formic acid and acetonitrile. Determination was performed using an AB SCIEX API 5000 triple quadrupole mass spectrometer (AB SCIEX, Concord, Ontario, Canada) and Analyst software version 1.6.2 (AB SCIEX, Concord, Ontario, Canada). In brief, 100 µL of each sample was placed in a polypropylene-tube. Samples were deproteinized with 200 µL acetonitrile (containing the internal standard piperacillin), subsequently vortex-shaked and centrifuged. The supernatant was further diluted with 0.01 M ammonium acetate buffer and 30 µL of each samples were injected into the LC-MS/MS system. The samples for cilastatin were detected with MRM (Multiple Reaction Monitoring) as follows: precursor → product ion for cilastatin 357.20 → 226.10 m/z and for piperacillin (internal standard) 516.20 → 329.90 m/z; for all analytes in negative mode. Under these conditions cilastatin and the internal standard eluted after approximately 1.8 and 2.2 minutes, respectively.

3.2.5. Dose adjustment

Dose adjustment was recommended if the imipenem trough concentration was below the target of 2 mg/L. Dose adjustment was performed, but could not exceed the maximum approved dose of 1000 mg / 1000 mg imipenem / cilastatin every 6 h. The smallest dose was 500 mg / 500 mg imipenem / cilastatin every 12 h. Due to the severity of infections in this study, we neither used 24 h dosing intervals nor the smallest 250 mg / 250 mg imipenem / cilastatin dose. In case of significantly accumulation of cilastatin, a switch to meropenem was considered. The attending physician ultimately decided whether dose adjustment was clinically warranted and performed.

3.2.6. Pharmacokinetic analysis

We considered one and two compartment models to describe the PK of imipenem and cilastatin. The prolonged infusion of imipenem and cilastatin was modelled as a time-delimited zero-order input rate into the respective compartment. Some of the peak concentrations occurred considerably after the end of the infusion.

To empirically describe the time-delay (*i.e.* a lag phase) between the start of the infusion and the drug passing through the infusion tubing, we included a series of ten transit compartments. The dead volume of the infusion tubing was approximately 17 mL.

Creatinine was modelled by a one-compartment model with a zero-order input rate to reflect natural creatinine synthesis. Glomerular filtration clearance (CL_{GFR}) at time zero, which is equivalent to creatinine clearance was calculated by the Cockcroft and Gault formula[96]. We modelled CL_{GFR} via a differential equation to allow CL_{GFR} to change during the study. Models with no, one, two, three or four changes of CL_{GFR} over time were considered. The half-life of change (TTURN) of CL_{GFR} and the time points of change (e.g. T1, T2 and T3) were estimated.

The glomerular filtration clearances of imipenem and cilastatin were calculated as the product of the unbound fraction (fu, 0.60 for cilastatin and 0.87 for imipenem) and the CL_{GFR} to account for plasma protein binding of cilastatin and imipenem. We assumed that the changes in renal function over time affected CL_{GFR} and renal tubular secretion (CLsec) to the same extent. This situation may arise, if the changes in both renal clearance mechanisms are determined by renal blood flow, for example. The time-dependence of $CL_{GFR}(t)$ is indicated by the "(t)" in the equations below. The CLsec was scaled by the $CL_{GFR}(t)$ calculated via the Cockcroft and Gault equation normalized to 4.5 L/h (equivalent to 75 mL/min). This scaling introduced the change of tubular secretion at times T1, T2 and T3.

Tubular secretion of imipenem and cilastatin was modelled either as a linear (i.e. first-order) or saturable (i.e. Michaelis-Menten) process. We considered models with a different population mean for the Michaelis-Menten constant (K_M) for patients with and without sepsis. As sepsis patients may have a poor renal function, the concentration of other compounds that are subject to tubular secretion may be higher and may therefore cause the K_M to be lower in sepsis patients. Nonrenal clearance (CL_{NR}) was modelled via a time-independent, first-order (i.e. non-saturable) process for each drug.

Therefore, the total clearances (CL_T) for imipenem and cilastatin contained terms for nonrenal clearance (CL_{NR}), tubular secretion clearance (CLsec) and

glomerular filtration. For models with a linear (i.e. non-saturable) tubular secretion clearance, CL_T was calculated as:

$$CL_T = CL_{NR} + CLsec \cdot \left(\frac{CL_{GFR}(t)}{4.5\,L/h} \right) + fu \cdot F_{Filt} \cdot CL_{GFR}(t) \qquad \textit{Equation 6}$$

Separate sets of parameter estimates for this equation were applied for imipenem and cilastatin. The factor F_{Filt} was included to account for a potential deviation of the glomerular filtration clearance of imipenem and cilastatin compared to the glomerular filtration clearance of creatinine. The F_{Filt} was fixed to a mean of 1.0 and its between subject variability was estimated. The same estimate was used for F_{Filt} of imipenem and cilastatin. For models that contained a saturable tubular secretion clearance (e.g. for cilastatin), the equation for total clearance was (c_{Cil}: cilastatin concentration in plasma):

$$CL_{T,Cil} = CL_{NR\,Cil} + \frac{CLsec_{Cil} \cdot Km_{Cil}}{Km_{Cil} + C_{Cil}} \cdot \left(\frac{CL_{GFR}(t)}{4.5\,L/h} \right) + fu_{Cil} \cdot F_{Filt} \cdot CL_{GFR}(t) \qquad \textit{Equation 7}$$

Overall, this model distinguished between nonrenal (CL_{NR}) and renal clearance by assuming that CL_{NR} was constant over time and not affected by CL_{GFR}. Renal clearance was split into two components, i.e. glomerular filtration and tubular secretion, which both changed over time. Glomerular filtration was calculated according to the Cockcroft and Gault formula with a (small) random deviation described by F_{Filt}. The remaining renal clearance was assumed to be due to tubular secretion. These assumptions allowed our model to estimate three different clearance components. Our modeling analysis was informed by a simultaneous fit of imipenem, cilastatin and serum creatinine concentrations.

3.2.7. Population estimation methodology

Nonlinear mixed-effects modeling of all data simultaneously was performed via the importance sampling algorithm (pmethod=4) in S-ADAPT (version 1.57)[97]. We utilized the SADAPT-TRAN facilitator tool for pre- and post-processing[98,99]. Between patient variability was described by log-normal distributions of all model parameters and residual error was described by an additive plus proportional model for each dependent variable. Model evaluation and selection was performed via standard population modeling procedures[100]. We carefully assessed all individual parameter

estimates for potential differences between patients with and without sepsis and between patients with poor, normal and good renal function. Descriptive statistics were calculated in WinNonlin Professional® (version 5.3, Pharsight, Cary, NC).

3.2.8. Non-compartmental analysis (NCA)

As the number of plasma samples within one dosing interval was very limited in this study, another approach for the calculation of the AUC than the trapezoidal method was needed. Firstly, we made the assumption, that in steady state, the amount of drug input is equal to the amount of drug elimination. Secondly, we assumed that after repeated dosing over four to five half-lives of a drug, steady state is achieved. Thirdly, we assumed that in steady state, the area under the curve after intermittent dosing equals the area under the curve after continuous infusion of the same amount of drug[101]. Finally, we assumed that the average (not the geometric mean) concentration after repeated dosing in steady state equals the steady state concentration after continuous infusion and therefore can be used to calculate the AUC using the following equation:

$$AUC = c_{av.}^{SS.} * \tau$$ *Equation 8*

Therefore, the means of the trough and peak plasma levels, dosages and the duration of the dosing intervals were calculated for each patient. With this data, the average concentration in steady state after repeated dosing was calculated using the following equation[102]:

$$c_{av.}^{SS.} = \frac{c_{\max}^{SS} - c_{\min}^{SS}}{\ln\left(\frac{c_{\max}^{SS}}{c_{\min}^{SS}}\right)}$$ *Equation 9*

With the resulting AUC and the mean dosage of each patient, the clearance of each individual was calculated using equation 5.

$$CL = \frac{Dose}{AUC}$$ *Equation 5*

Finally, the resulting CL was correlated with renal function, expressed by CL_{GFR} (estimated by the Cockcroft and Gault formula) and was compared with CL obtained by the population pharmacokinetic approach.

3.3. Results

This study included 66 ICU patients with a median baseline creatinine clearance of 73.1 (range: 4.9 to 223) mL/min according to the Cockcroft & Gault formula (Table 3-1). Patients received an average number of 14 imipenem / cilastatin doses [range 3 to 29]. In total, 524 plasma concentrations of imipenem and 522 plasma concentrations of cilastatin were available with a median [5th to 95th percentile] of 9 [2 to 14] samples per patient.

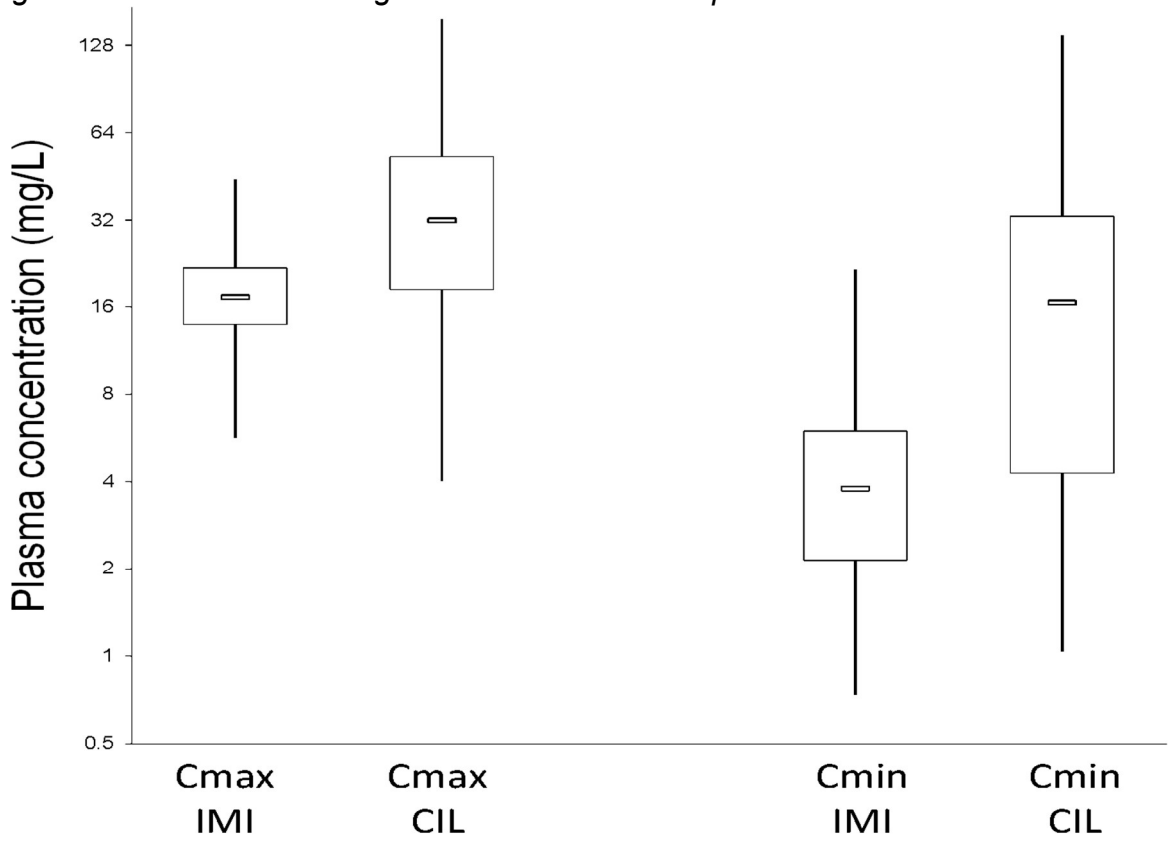
Table 3-1 Population characteristics

Parameter	**Value [median (range) or No. (%)]**	
No.	66	
Age (yr)	66	(19 - 90)
Total body weight (kg)	80	(50 - 130)
Height (cm)	172	(150 - 192)
Body mass index (kg/m²)	26.1	(16.0 - 45.0)
Sex		
Male	42	(63.6)
Female	24	(36.4)
Baseline serum creatinine (mg/dL)	1.07	(0.42 - 15.0)
Baseline creatinine clearance by Cockcroft & Gault (mL/min)	73.1	(4.9 - 223)
Sepsis		
No	10	(15.2)
Yes	56	(84.8)
Septic shock	51	(77.3)

Peak concentrations after a 3-h infusion were 18.7 ± 7.0 mg/L for imipenem and 39.1 ± 26.5 mg/L for cilastatin (average ± SD); and trough concentrations were 4.79 ± 3.62 mg/L (range: <0.5 mg/L [below quantification limit] to 21.7 mg/L) for imipenem and 22.6 ± 24.4 mg/L for cilastatin (range: <0.5 mg/L [below quantification limit] to 138.5 mg/L).

Twenty-six patients (39.4%) included in our TDM program failed to reach target plasma concentrations of imipenem and nine patients (13.6%) showed significantly increased cilastatin concentrations above 50 mg/L (Figure 3-1). Based on these results, dose adjustment was performed in eight patients (12.1%) for imipenem / cilastatin; four patients (6.1%) were switched from imipenem / cilastatin to meropenem.

Figure 3-1 Peak and trough concentrations of imipenem and cilastatin.



The dash represents the median, boxes the interquartile range, and whiskers the minimum and maximum.

3.3.1. Results of the population pharmacokinetic analysis

A one-compartment model for our prolonged infusion data with relatively sparse sampling adequately described the PK of imipenem and cilastatin. The final model provided adequate curve fits for the simultaneous fit of imipenem, cilastatin, and the serum creatinine concentration as shown in Figure 3-2, where concentration vs time plots for 16 exemplary patients are shown. Observed concentrations are represented by dots and curves represent the individually fitted concentrations. In Figure 3-3, individual fits and population fits for all three substances are shown.

Figure 3-2 Individual fitted imipenem, cilastatin, and serum creatinine concentrations.

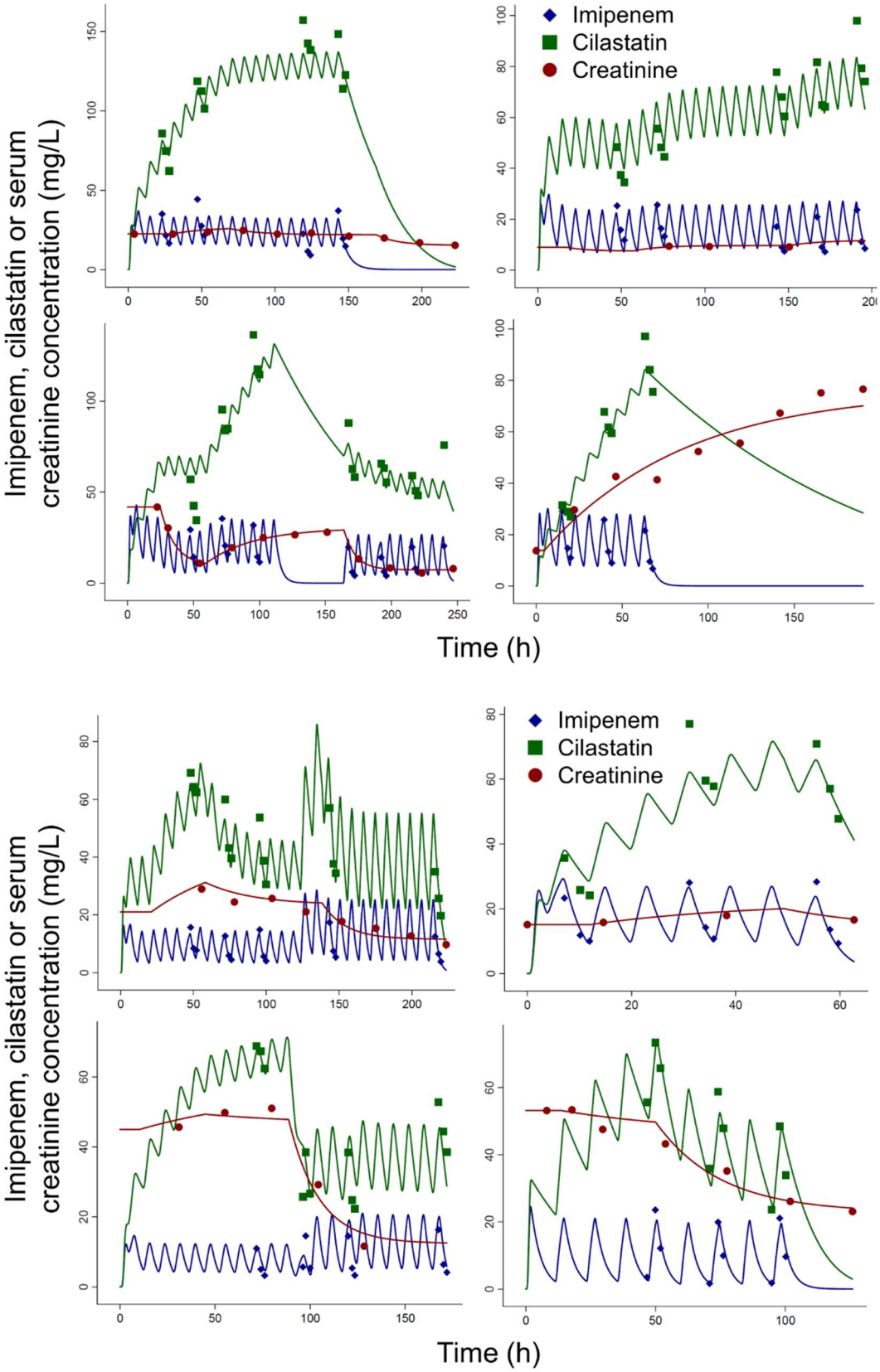


Figure 3-2 continued

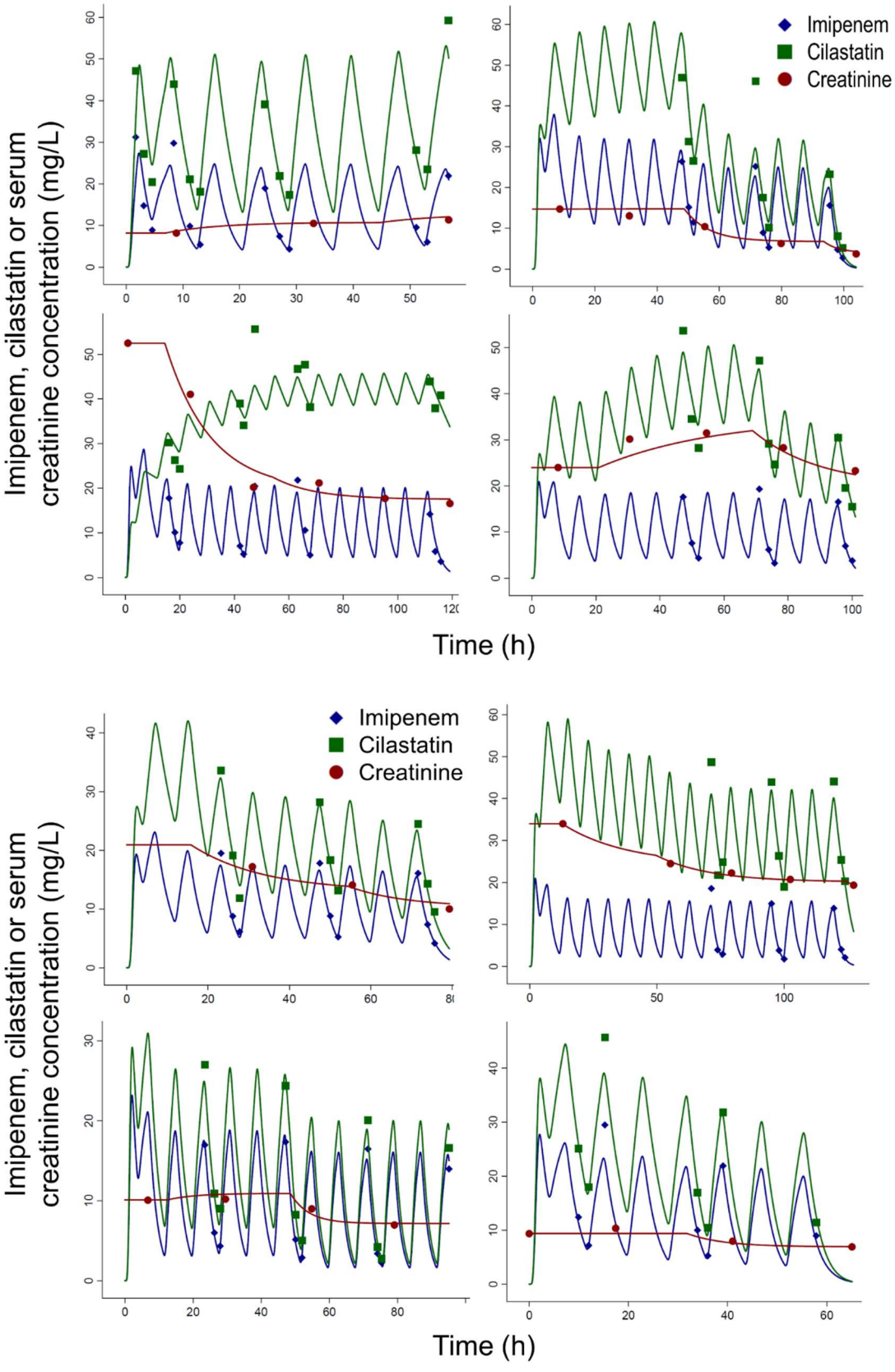
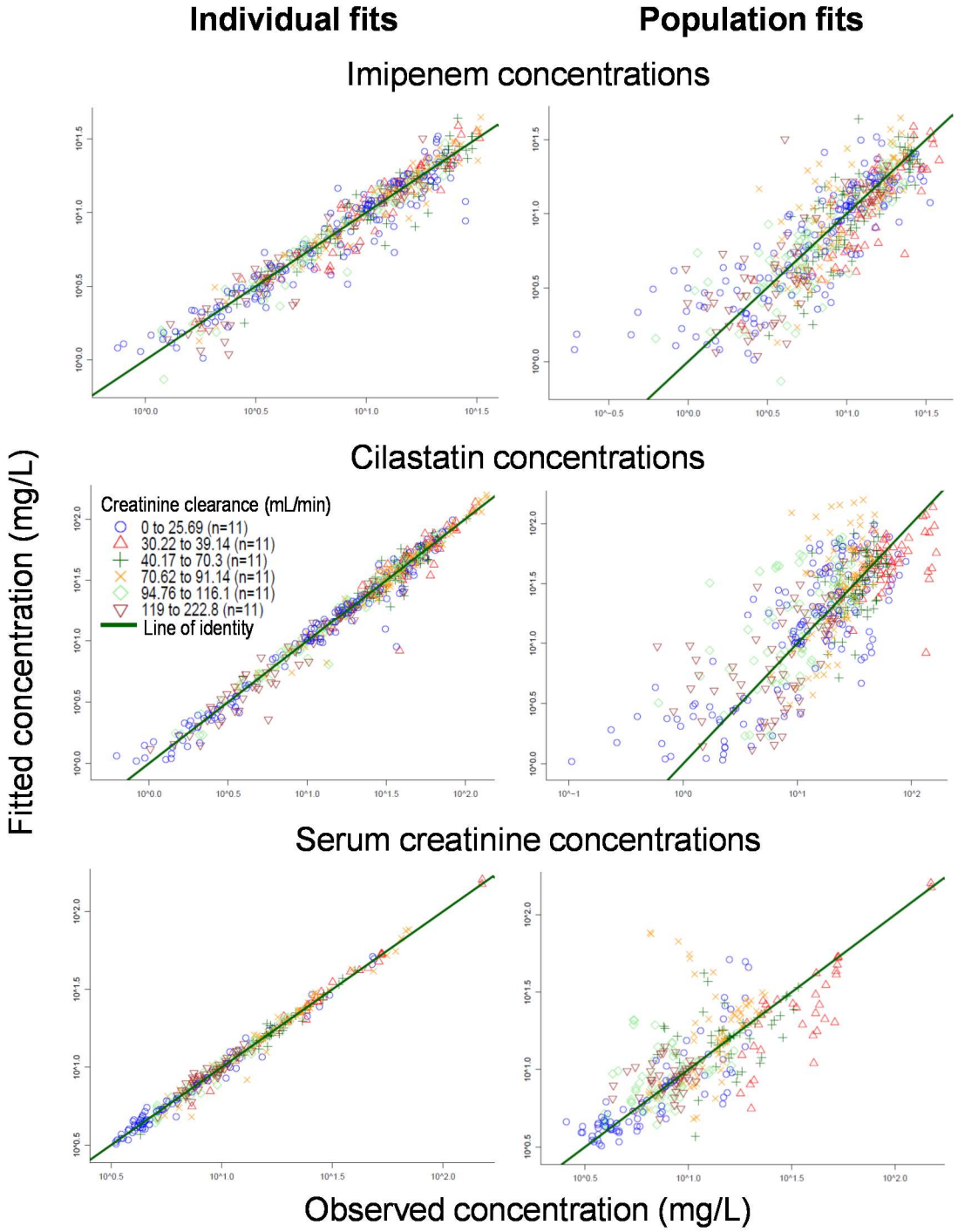


Figure 3-3 Observed vs. individual (left side) or population fitted (right side) concentrations for imipenem, cilastatin, and serum creatinine.

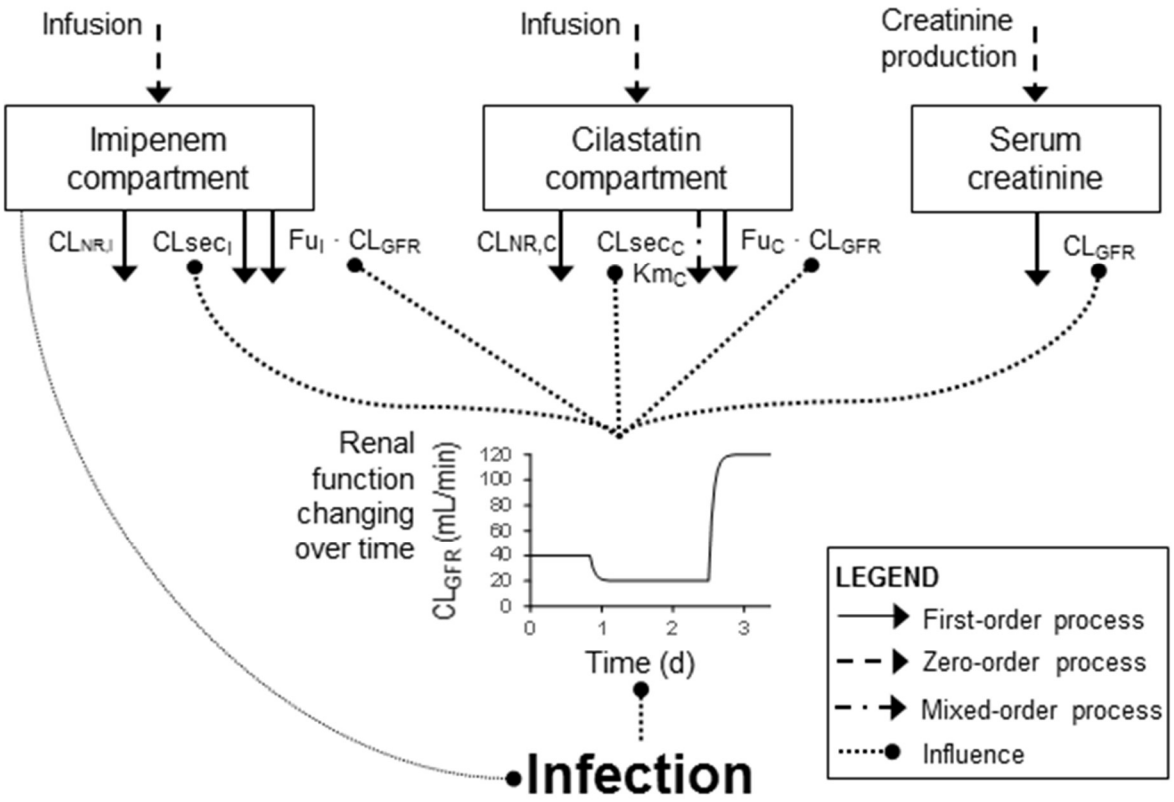
95



In the model, total clearance was comprised of nonrenal clearance, glomerular filtration, and renal tubular secretion (Figure 3-4). We assumed that glomerular filtration and tubular secretion were proportional to creatinine clearance, whereas nonrenal

clearance was independent of creatinine clearance. This allowed us to distinguish between the nonrenal and renal clearance components in the model.

Figure 3-4 Structural model for imipenem, cilastatin and serum creatinine.



An infection can lead to substantial and rapid changes of renal function (*i.e.* glomerular filtration and tubular secretion) over time. In the population PK model, renal function affected the glomerular filtration of imipenem, cilastatin and creatinine and tubular secretion of imipenem and cilastatin. Nonrenal clearance of imipenem and cilastatin were constant over time (i.e. not affected by changes in renal function).

Nonrenal clearance was assumed to be constant over time and to be on average the same in septic and non-septic patients. Nonrenal clearance was estimated to be much larger for imipenem (geometric mean: 5.30 L/h, 24.9% coefficient of variation [CV] for between patient variability) than for cilastatin (0.138 L/h, 33.3% CV). This was clinically highly important, since it led to accumulation of cilastatin but not of imipenem concentrations in patients with poor renal function.

Renal clearance contained glomerular filtration and tubular secretion (see Figure 3-4). We assumed that only unbound drug was available for glomerular filtration and accounted for the 13% protein binding of imipenem[52] and 40% protein binding of cilastatin[51]. Tubular secretion was assumed not to be affected by protein binding. However, based on the intact nephron hypothesis, we assumed that tubular secretion was linearly correlated with creatinine clearance.

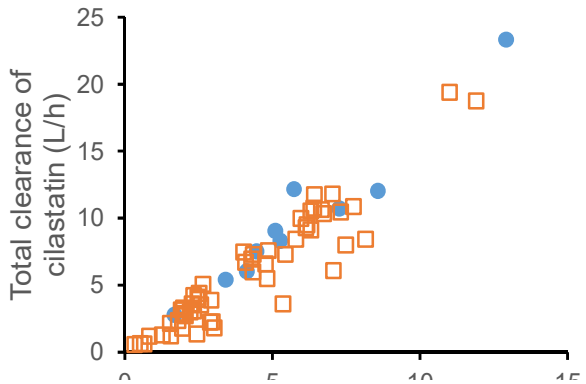
We allowed renal function to change over time in our critically ill patients and explored models with no, one, two, three, or four changes of renal function during the study period. Models with no, one or two change(s) of renal function over time were significantly inferior to a model with three changes of renal function. Including a fourth change of renal function yielded no meaningful improvement in the curve fits or the objective function. Therefore, the model with three changes of renal function over time was chosen as the final model. While renal function changed rapidly (the associated half-life, TTURN, was eventually fixed to 5 min), it could take several days until serum creatinine concentration achieved steady state (Figure 3-2). The first change of renal function was estimated to occur at 16.2 h (2.85 to 31.6 h; median (range)), the second change at 54.1 h (33.3 to 78.3 h), and the third change at 140 h (88.5 to 222 h).

The tubular secretion clearance of imipenem was relatively small (1.29 L/h; 14.3% CV) and not saturable. In contrast, the tubular secretion clearance of cilastatin was more substantial (4.87 L/h; 8.84% CV) and could be saturated by high cilastatin concentrations. Interestingly, the Michaelis-Menten constant (K_M) was considerably smaller and much more variable in patients with sepsis (50.6 mg/L; 153% CV) compared to patients without sepsis (219 mg/L; 46.0% CV). Therefore, cilastatin tubular secretion was more saturated in septic compared to non-septic patients.

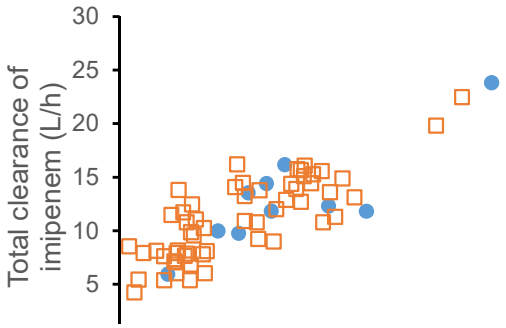
The total clearance of imipenem, cilastatin and creatinine (glomerular filtration rate) were linearly correlated (Figure 3-5). The estimated total clearance of cilastatin approached 0 L/h for patients with poor renal function, since nonrenal clearance of cilastatin was estimated to be very small. In contrast, the total clearance of imipenem was above 4 L/h in all patients due to the nonrenal clearance. While cilastatin was almost exclusively renally eliminated, imipenem had a significant nonrenal clearance component in all patients.

Figure 3-5 Correlation plots of a) cilastatin clearance vs. glomerular filtration rate (i.e. creatinine clearance), b) imipenem clearance vs. glomerular filtration rate, and c) cilastatin clearance vs. imipenem clearance in patients with (red squares) and without (blue dots) sepsis.

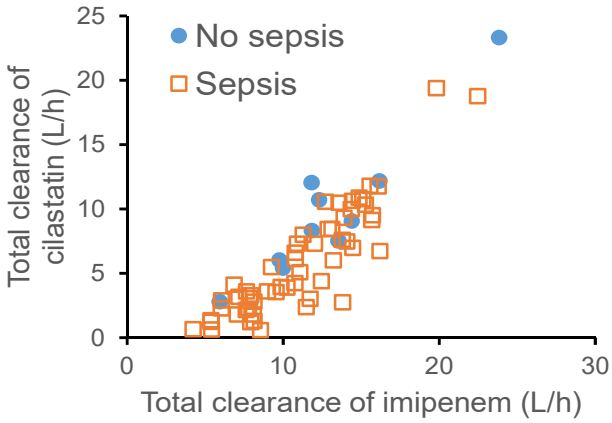
a)



b)



c)

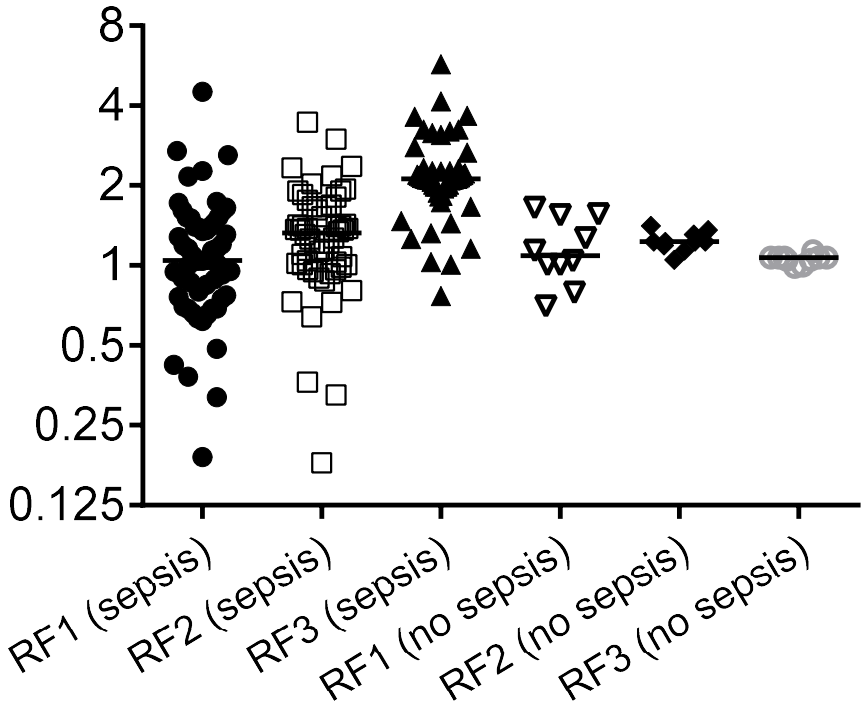


For patients with 70 kg total body weight, volume of distribution was 24.9 L (20.6% CV) for imipenem and 23.1 L (45.1% CV) for cilastatin. After accounting for the effect of body weight, the individual estimates for volume of distribution (mean [range]) in our patients were 28.8 L [14.9 to 50.2 L] for imipenem and 25.1 L [10.2 to 80.4 L] for cilastatin. Total clearance was 11.6 L/h [4.24 to 27.5 L/h] for imipenem and 6.14 L/h [0.520 to 26.6 L/h] for cilastatin. The cilastatin tubular secretion clearance was calculated assuming an average cilastatin concentration of 20 mg/L. Due to the saturation of tubular secretion, higher cilastatin concentrations would yield a slightly

lower clearance. The resulting terminal half-lives were 1.72 h [0.843 to 4.05 h] for imipenem and 2.75 h [0.538 to 95.6 h] for cilastatin.

The factors RF1, RF2 and RF3 describe the ratio of renal function after the respective change compared to the baseline renal function at time zero. The changes of renal function over time were substantial in patients with sepsis. The coefficients of variation for the between patient variability of RF1, RF2 and RF3 ranged from 53.7 to 62.9% in patients with sepsis and was much smaller (<30%) in patients without sepsis (Figure 3-6). This suggested that renal function was relatively stable in patients without sepsis.

Figure 3-6 Fractional changes in renal function after the first (RF1), second (RF2) and third change time (RF3).



The left three columns refer to patients with sepsis or septic shock and the right two columns to patients without sepsis. The markers are the individual estimates in each patient and the bar represents the median. A value of 1.0 represents an unchanged renal clearance.

Table 3-2 Population pharmacokinetic parameter estimates for imipenem, cilastatin and renal function.

Parameter	Symbol	Unit	Population mean	Between subject variability (CV)
Volume of distribution of central compartment for imipenem	V_{1I}	L	24.9 [a]	20.6%
Volume of distribution of central compartment for cilastatin	V_{1C}	L	23.1 [a]	45.1%
Nonrenal clearance of imipenem	$CL_{NR,I}$	L/h	5.30 [a]	24.9%
Nonrenal clearance of cilastatin	$CL_{NR,C}$	L/h	0.138 [a]	33.3%
Tubular secretion clearance of imipenem (not saturable)	$CLsec_I$	L/h	1.29 [a,b]	14.3%
Tubular secretion clearance of cilastatin (saturable)	$CLsec_C$	L/h	4.87 [a,b]	8.84%
Michaelis-Menten constant for tubular secretion clearance of cilastatin in patients with or without sepsis	K_Msec_C (sepsis)	mg/L	50.6	153%
	K_Msec_C (no sepsis)	mg/L	219	46.0%
Glomerular filtration rate at time zero	CL_{GFR}	L/h	4.64 [c]	60.5% [c]
Ratio of imipenem and cilastatin renal filtration clearance divided by CL_{GFR}	F_{Filt}		1 (fixed)	34.9%
Fractional change in renal function at time T1 in patients with sepsis	$RF1_{SEP}$		1.05	55.9%
Fractional change in renal function at time T2 in patients with sepsis	$RF2_{SEP}$		1.36	62.9%
Fractional change in renal function at time T3 in patients with sepsis	$RF3_{SEP}$		2.11	53.7%
Fractional change in renal function at time T1 in patients without sepsis	$RF1_{NO}$		1.11	28.1%
Fractional change in renal function at time T2 in patients without sepsis	$RF2_{NO}$		1.23	11.0%
Fractional change in renal function at time T3 in patients without sepsis	$RF3_{NO}$		1.07	7.24%
Half-life for the rate of change of glomerular filtration	TTURN	min	5	0% (fixed)
Time of first change of renal function	T1	h	15.9	64.1%
Time gap between the first and second change in renal function	T2 - T1	h	37.7	15.1%
Time gap between the second and third change in renal function	T3 - T2	h	85.6	35.0%

[a]: Population mean for a patient with 70 kg total body weight using an allometrically scaled body size model.

[b]: This estimate was linearly scaled via the glomerular filtration rate normalized to a value of 4.5 L/h.

[c]: This estimate represents the glomerular filtration rate calculated via the Cockcroft and Gault (i.e. this is not an estimated model parameter).

3.3.2. Results of the non-compartmental analysis

Three patients were excluded from the analysis due to missing trough or peak plasma samples.

The resulting mean ± SD Cmax and Cmin of all remaining patients were 18.4 ± 6.1 µg/mL and 4.3 ± 3.0 µg/mL for imipenem and 38.3 ± 23.4 and 18.8 ± 23.1 µg/mL for cilastatin. This data resulted in an average steady state concentration of 9.5 ± 4.3 µg/mL for imipenem and 27.0 ± 22.7 µg/mL for cilastatin. The average duration of an infusion interval was 7.9 h.

The resulting mean ± SD AUC and CL was 75.4 ± 34.2 µg*h/mL and 15.5 ± 7.3 L/h for imipenem and 216.2 ± 184.9 µg*h/mL and 10.1 ± 9.9 L/h for cilastatin.

Imipenem and cilastatin CL were in good correlation with creatinine clearance, showing correlation coefficients (r) of 0.812 ($p<0.001$) and 0.863 ($p<0.001$). Graphical representations of these correlations are shown in Figure 3-7 and 3-8. These correlation plots show also, that imipenem has, in contrast to cilastatin, a significant proportion of nonrenal clearance, which is approximately 5 to 6 L/h.

Figure 3-7 Correlation plot of imipenem clearance vs. creatinine clearance.

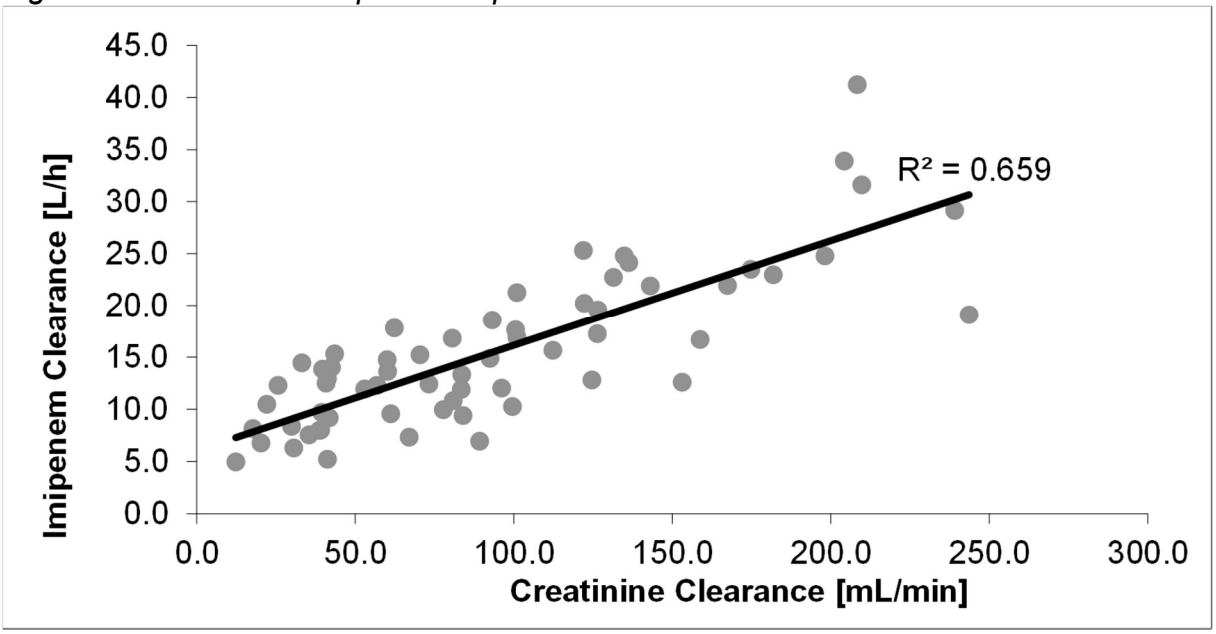
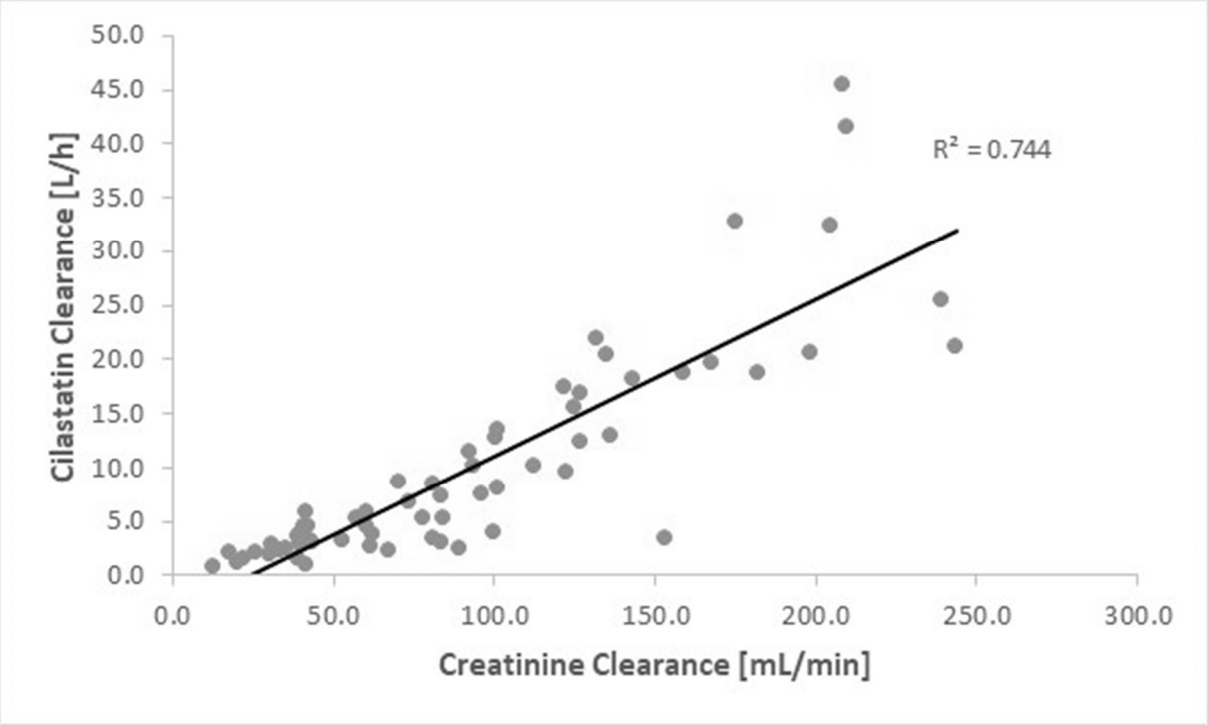


Figure 3-8 Correlation plot of cilastatin clearance vs. creatinine clearance.



Imipenem and cilastatin CL obtained by non-compartmental analysis (NCA) correlated well with CL obtained by the population pharmacokinetic (POP-PK) approach, resulting in correlation coefficients (r) of 0.882 ($p<0.001$) and 0.908 ($p<0.001$). However, the NCA seems to produce systematically higher results for CL than the POP-PK approach, which is also reflected by the slope of the regression line in Figure 3-9 (imipenem) and Figure 3-10 (cilastatin). Thus, it can be concluded that the higher the CL of imipenem and cilastatin, the more differ the results of the NCA to the results of the POP-PK approach.

Figure 3-9 Correlation plot of imipenem clearance (POP-PK) vs. imipenem clearance (NCA).

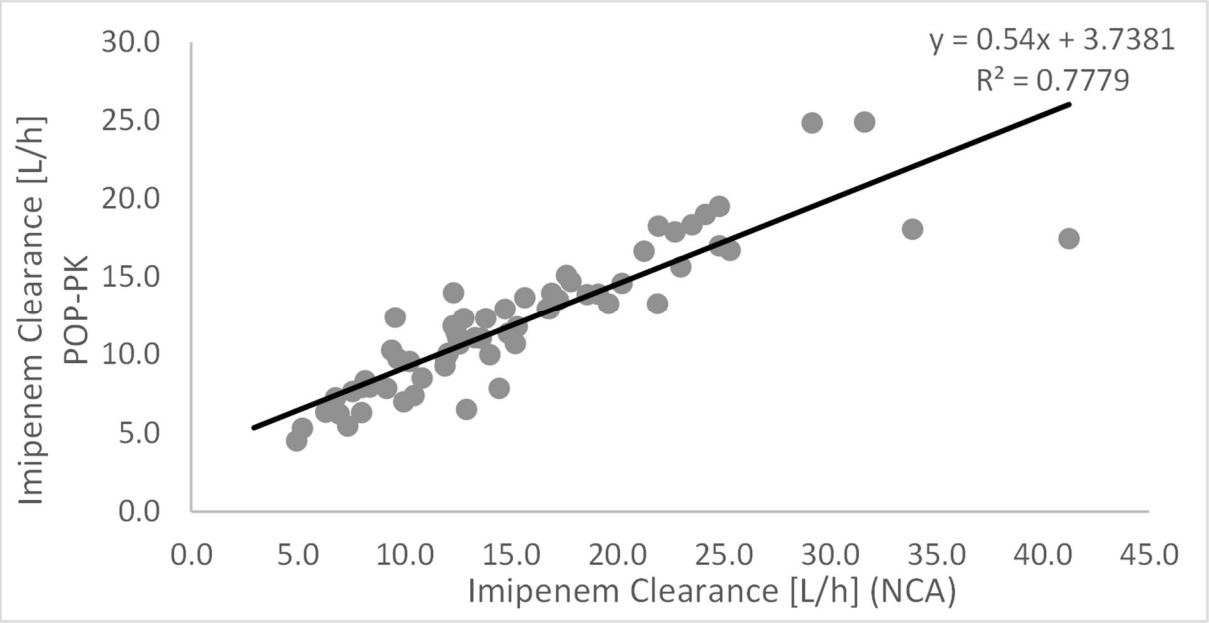
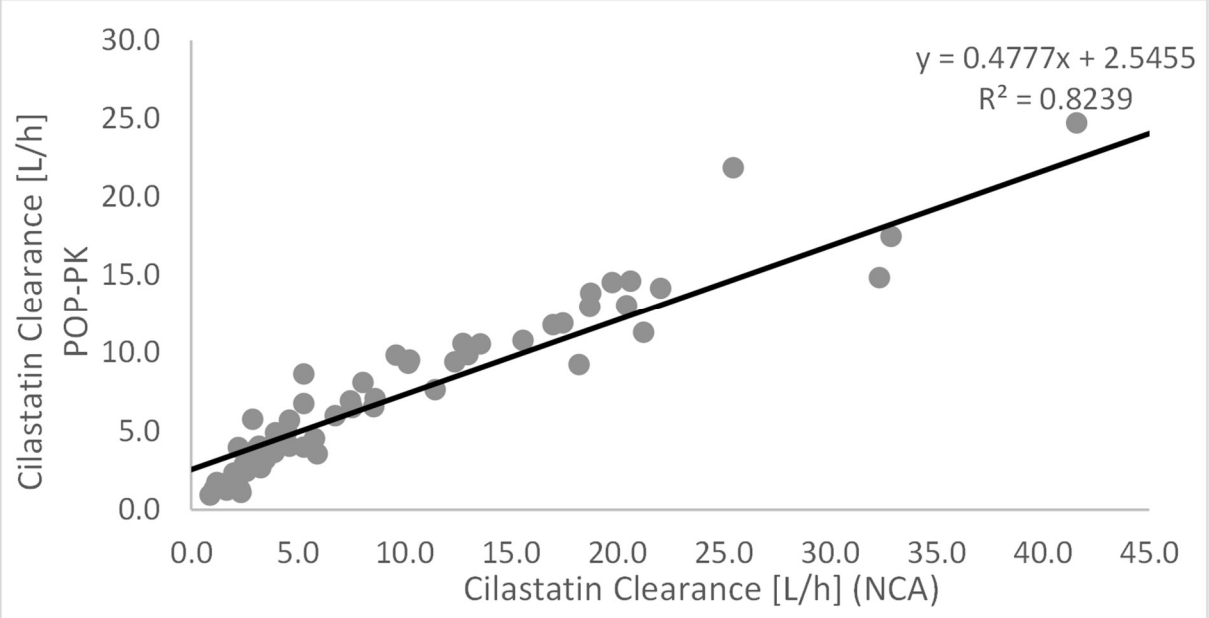


Figure 3-10 Correlation plot of cilastatin clearance (POP-PK) vs. cilastatin clearance (NCA).



3.4. Discussion

This study presents the first population PK analysis for imipenem and cilastatin in a large group of ICU patients and highlighted a substantial need for TDM of imipenem and cilastatin, particularly for patients with sepsis and altered renal function.

This study identified and estimated significant differences in the overall contributions to clearance of imipenem and cilastatin in patients. Altered renal function substantially affected the total clearance of cilastatin which was almost exclusively renally cleared. Therefore, patients with poor renal function were shown to experience significant accumulation of cilastatin (Figure 3-2). Furthermore, renal tubular secretion of cilastatin was saturable with a 4-fold lower Km in septic patients compared to non-septic patients. This led to further accumulation of cilastatin in patients with sepsis. The nonrenal clearance of imipenem (5.30 L/h = 88.3 mL/min) was much larger than that of cilastatin (0.138 L/h = 2.3 mL/min). Thus, significant accumulation of imipenem did not occur even in patients with poor renal function.

As expected, the between patient variability of the plasma concentrations and clearance was substantially larger in patients with sepsis compared to patients without sepsis (Figure 3-5). Additionally, the within-patient variability of renal function was very high in patients with sepsis as indicated by the changes of renal function during the treatment period (Figure 3-6). While renal function and therefore renal clearance of imipenem and cilastatin was estimated to change rapidly (within <1 h; see TTURN in Table 3-2), it could take several days for creatinine concentrations to reach their new steady-state (Figure 3-2). Therefore, the assumption of the Cockcroft and Gault formula of creatinine being at steady-state is likely violated in septic patients.

The large between patient and within patient variability in patients with sepsis suggested a strong benefit to individualize imipenem / cilastatin doses to achieve and maintain safe and effective concentrations. Given the severity of infections in critically ill patients, the ability to optimize doses rapidly is critical in these patients[103]. As creatinine only achieved its steady-state slowly and may not be at steady-state during the first days of therapy, dose adjustment based on creatinine concentrations may result in suboptimal antibiotic concentrations. The antibiotic concentrations during the first day(s) of therapy are likely critical for optimal outcomes[104]. Without dose individualization, 39.4% of patients in this study failed to reach target concentrations of imipenem and nine patients (13.6%) showed significant increased cilastatin concentrations above 50 mg/L (Figure 3-1 and Figure 3-2).

Measuring imipenem and cilastatin concentrations directly and performing dose adjustments presents a highly promising approach of TDM to assure effective and safe

concentrations both during initial and maintenance therapy. This study strongly suggested that TDM of imipenem / cilastatin needs to serve two purposes; assuring that effective imipenem concentrations are reached and that cilastatin concentrations do not accumulate substantially.

Therefore, a simple dose adjustment based on renal function that optimizes the plasma concentrations of both imipenem and cilastatin is unfortunately not possible in patients with a wide range of renal function. While dose adjustment can achieve reasonable success for patients with moderate and high renal function, patients with poor renal function are problematic. In the latter patients, a normal dose will achieve adequate imipenem concentrations and likely lead to substantial accumulation of cilastatin; a small dose will minimize the accumulation of cilastatin, but likely yield sub-therapeutic concentrations of imipenem. Optimal dosing of patients with poor renal function would require an imipenem / cilastatin combination with a smaller proportion of cilastatin than the currently marketed 1:1 combination[105].

If no TDM is available for imipenem and cilastatin, it may be preferable to use an alternative antibiotic, such as meropenem, for dosing of patients with poor renal function (glomerular filtration rate below 3 L/h, equivalent to 50 mL/min). In these patients, accumulation of cilastatin usually required over 24 h. Therefore, dosing imipenem/cilastatin during the first day of therapy is not expected to yield substantial accumulation of cilastatin.

In contrast, patients with high renal function may require daily doses larger than the maximum approved dose of 4 g / 4 g imipenem / cilastatin to achieve effective imipenem concentrations. We are not aware of systematic studies which assessed the safety, including the risk for seizures, of such high imipenem / cilastatin doses. However, if the plasma concentrations are associated with adverse events, TDM should be useful for dose selection in patients with normal and high renal function.

In our study, TDM results were available within 12 to 24 h which is sufficient to make an informed dosing decision on the next day, *i.e.* before cilastatin accumulation likely becomes extensive. Therefore, this study shows that TDM of imipenem and cilastatin is feasible, if the assays for imipenem and cilastatin are established at the respective laboratory.

Our population modeling showed that a one compartment model was sufficient to describe the PK of imipenem and cilastatin after a prolonged infusion. Our model accounted for up to three changes in renal function during therapy and provided adequate individual and population fits (Figure 3-2 and Figure 3-3). While prior modeling analyses utilized multi-compartment models for imipenem given as short-term infusions[63–66,71,72,74–76], the longer infusion duration and relatively sparse sampling in our study likely led to a one-compartment model being sufficient for our dataset. For imipenem, our estimates for clearance and volume of distribution at steady-state were in good agreement with the median of the clearance and volume of distribution estimates from other studies in ICU patients (Figure 2-8 and Figure 2-9). For cilastatin, our estimated volume of distribution at steady-state was within the range of previously reported values (Figure 2-9). Published studies in ICU patients on cilastatin assessed either patients with severe renal impairment (including failure) or a healthy volunteer control group[64–67]. Our estimated total clearance of cilastatin in ICU patients with a wide range of renal function fell between the estimates from previous studies. Importantly, the between patient variability of the apparent terminal half-life was extremely wide with a median [range] of 2.75 h [0.538 to 95.6 h] for cilastatin. Due to the large nonrenal clearance of imipenem, the variability of terminal half-life was much more narrow (1.72 h [0.843 to 4.05 h]) for imipenem.

The results of the non-compartmental PK analysis of imipenem and cilastatin plasma levels demonstrate that this straightforward method can provide reliable PK results even with scarce data.

However, several limitations of this approach should be considered. Firstly, the calculation of the average steady state concentration using equation 11 is only applicable in steady state conditions and a minimum of one peak and one trough plasma level per individual is necessary. Moreover, the peak and trough blood samples have to be collected as quickly as possible after the end of the infusion and directly before the start of the next infusion to provide reliable average steady state plasma concentrations. However, if drugs with short half-life as imipenem and cilastatin are administered as prolonged infusions, steady state may be reached after few infusions and peak concentrations do not fluctuate as much as after short infusions.

Secondly, the comparison with the results of the POP-PK approach show that the NCA approach tends to overestimate the clearances of imipenem and cilastatin, particularly for high clearances.

Finally, the NCA approach does not provide results for half-life and volume of distribution, as the elimination rate constant (ke) cannot be determined reliably with only one peak and one trough plasma level.

3.5. Conclusion

Cilastatin showed substantial accumulation in septic patients with poor renal function, since cilastatin was predominantly renally eliminated. Additionally, renal tubular secretion of cilastatin, but not of imipenem, was saturable. Imipenem showed much less accumulation, since its nonrenal clearance was much larger than that of cilastatin. In patients with poor renal function, accumulation of cilastatin may present a safety concern and it does not seem possible to simultaneously optimize imipenem and cilastatin doses for patients with diverse renal function. As the between patient and within patient variability of imipenem and cilastatin was substantial, TDM of imipenem and cilastatin provides a feasible and timely approach to optimize doses in ICU patients. Future studies are warranted to develop individualized dosing algorithms and show improved outcomes for ICU patients with and without TDM of imipenem and cilastatin.

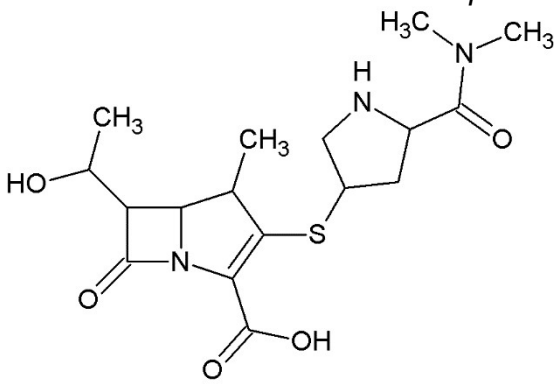
4. Overview of pharmacokinetic studies of meropenem in critically ill patients and healthy volunteers

4.1. Introduction

4.1.1. Chemistry of meropenem

The empirical formula of meropenem is $C_{17}H_{25}N_3O_5S$ and the structural formula of meropenem is shown in Figure 4-1. Meropenem has a molecular weight of 383.5 g/mol. Meropenem is an organic acid with a pKa of 2.9[106]. At physiological pH, it is highly ionized and hydrophilic as expressed by a logD value of -3.74 at pH 7[51].

Figure 4-1 Structural formula of meropenem.



4.1.2. Indication and dosing of meropenem

Meropenem is a parenteral broad spectrum member of the carbapenem class of the beta-lactam antibiotics. It is used in the treatment of severe infections caused by Gram-positive and Gram-negative organisms, including beta-lactamase producing bacteria and anaerobes. Meropenem is approved for the treatment of pneumonia, including community-acquired and hospital-acquired pneumonia, broncho-pulmonary infections in cystic fibrosis, complicated infections of the kidney and the urinary tract, complicated intra-abdominal infections, intra- and post-partum infections, complicated skin and soft tissue infections and acute bacterial meningitis[107]. The dosage recommendations for skin and skin structure infections are 500 mg given every 8 hours and for intra-abdominal infections 1 g given every 8 hours. Treating complicated skin and skin structure infections caused by Pseudomonas aeruginosa, a dose of 1 g every 8 hours is recommended[108]. According to the prescribing information, meropenem is administered only intravenously as bolus injection or short time infusion. However,

alternative administration regimens in order to attain higher trough levels, namely prolonged infusion or even continuous infusion were proposed from several authors[44,109–114].

4.1.3. Distribution and elimination of meropenem

The plasma protein binding of meropenem is very low, only about 2 % of meropenem is bound to plasma proteins[115]. The distribution of meropenem has been studied in a variety of tissues of the human body and is rapidly and substantial[45]. As the underlying diagnoses of patients in a surgical intensive care unit were mainly abdominal infections and pneumonia, each with or without blood stream infection, the penetration of meropenem in these tissues is of particular interest in terms of the determination of target plasma levels for meropenem.

Several studies have examined the pharmacokinetics of meropenem in lung tissues. The most recent[116] examined the penetration of meropenem into epithelial lining fluid (ELF) of patients with ventilator-associated pneumonia and estimated the median penetration ratio (AUC_{ELF}/AUC_{Plasma}) to be about 25 %. However, a large variability was reported. Another study reported ELF and alveolar cell to plasma penetration ratios of meropenem to be in the range of 32 % to 53 % and 26 % to 34 % respectively[45,117]. Other research, which explored tissue penetration of meropenem using microdialysis technique revealed a penetration ratio of interstitial lung tissue to plasma of about 20%[118].

Studies investigating the penetration of meropenem in abdominal tissues suggest that the concentrations obtained in abdominal tissues are higher than the levels achieved in the lung. For instance, Condon et al.[119] found meropenem concentrations of 12.2 µg/mL in peritoneal fluid approximately one hour after administration of meropenem, corresponding to a penetration ratio of about 45 %. Karjagin et al. found a peritoneal tissue to plasma penetration ratio of about 74 %[120]. With the exception of peak levels, Ikawa et al.[121] who used population pharmacokinetic methods even observed higher concentrations of meropenem in peritoneal fluid than in plasma after the administration of 0.5 g meropenem.

Meropenem is mainly excreted via the renal route and therefore renal impairment leads to significant prolongation of the elimination half-life. In subjects with normal renal function, half-life of meropenem is about 1 h, and the volume of

distribution at a steady state ranges from 11.7 to 26.6 L[122]. In patients with compromised renal function, the half-life can range from 1.5 to 6 h depending on the degree of renal dysfunction[123,124]. Between creatinine clearance and meropenem clearance, there exists a linear correlation, and nonrenal excretion increases as renal function declines[125]. According to the prescribing information, dose adjustment for patients with impaired liver function is not necessary[107]. This statement is supported by Thyrum et al., who conducted a study on the pharmacokinetics of meropenem in patients with alcoholic liver cirrhosis[126]. They found no statistically significant difference in pharmacokinetic parameters of meropenem and its metabolite between patients with liver disease and matched controls. Moreover, meropenem was tolerated well in both groups.

4.1.4. PK/PD - targets of meropenem

Preclinical data suggest that for the achievement of maximal bactericidal effect, the concentration of carbapenem antibiotics should exceed the MIC of the pathogen for 40 % of the dosing interval[45,58]. However, the PK/PD-target may be significantly higher under clinical conditions. Reasons for this are the clinical situation of the patient, the focus of the infection and whether further targets, such as the prevention of resistant strains of the pathogen should be achieved.

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database Version 6.0[60], the PK/PD breakpoints for susceptible bacteria as pseudomonas spp. and enterococcus spp. are ≤ 2 µg/mL. In light of these data and with respect to tissue penetration factors, Tröger et al. suggested a therapeutic range of meropenem of 4 to 10 µg/mL for trough levels, to ensure concentrations of 4 to 5 times the MIC at least across 60 % of the dosing interval[127]. Pea et al. even supposed a Cmin/MIC ratio of 4 to 6, which could maximize the effectiveness of meropenem, either in terms of clinical outcome or in terms of prevention of resistance spread[128].

A recent survey of beta-lactam antibiotic TDM practice in intensive care units[129] listed PK/PD targets for dose adaption. Targets differed significantly between the different institutions. While some targeted 100 % T > MIC, others targeted 40 % T > 4x MIC or even 100 % T > 4 x MIC.

4.2. Methods

4.2.1. Literature search for pharmacokinetic studies of meropenem in critically ill patients

A literature search in the PubMed database was performed using the algorithm "meropenem AND (plasma OR serum) AND (concentration OR microg/mL OR mg/mL) AND (intensive care unit OR ICU OR critically ill OR sepsis OR septic shock OR ventilator associated pneumonia OR VAP)". Search filters were set to “humans”, “Adult: 19+ years” and “English”, “French” or “German” language. Thereafter, a hand search was performed, in which the references of the previously obtained papers were searched for relevant articles. The resulting papers were searched for plasma level and PK data of meropenem in critically ill patients.

4.2.2. Literature search for pharmacokinetic studies of meropenem in healthy volunteers

For comparison of the pharmacokinetics of meropenem in critically ill patients with healthy volunteers, a second literature search in the PubMed database was performed using the algorithm “meropenem pharmacokinetics healthy”. Search filters were set to “English”, “French” or “German” language. The resulting papers were searched for plasma level and PK data of meropenem in healthy volunteers.

4.2.3. Data preparation and presentation

The studies were searched for information about the study population (clinical situation, number and demographical data of patients), drug administration (dosage and route of administration) and resulting pharmacokinetic data of meropenem. If necessary, data was converted into standardized units ($t_{1/2}$: hours, AUC: µg*h/mL, CL: L/h and Vd: L) and was extrapolated to the mean body weight of the respective study participants.

4.3. Results and Discussion

4.3.1. Results of the PubMed search

The PubMed search for PK data of meropenem in critically ill patients resulted in forty-seven hits and the subsequent hand search resulted in five additional papers.

Sixteen papers were excluded since these did not provide plasma or serum levels or pharmacokinetic data of meropenem or were case reports. One study[130] was excluded despite reporting trough plasma levels of meropenem and other antibiotics, as the clinical data were not separated by antibiotic.

The PubMed search for literature data of meropenem pharmacokinetics in healthy volunteers resulted in forty-six hits. Thirty-one papers were excluded since these did not provide plasma/serum levels or pharmacokinetic data of meropenem in healthy volunteers.

4.3.2. Literature data of meropenem pharmacokinetics in critically ill patients

Overall, thirty-five studies on the pharmacokinetics of meropenem in critically ill patients were included in this overview. The most recent papers were from 2017, the oldest date back to 1999. The number of patients differed greatly between the studies, with a median of 15 participants (range 5 to 481). One study[131] reported the results of 74 sample series of a drug-monitoring program for meropenem; however, the corresponding number of patients was not given.

An overview of these studies and the resulting pharmacokinetic parameters of meropenem is provided in Table 4-1. The trough and peak plasma concentrations of meropenem from the different studies are compared and illustrated in Figure 4-2 and 4-3.

All studies included in this overview investigated the pharmacokinetics of meropenem in critically ill patients. However, a number of studies focused on specific subgroups. Overall, seven studies set the inclusion criteria to patients with severe sepsis or septic shock[109,120,132–136], two studies focused on neutropenic patients[137,138] two studies investigated the pharmacokinetics of patients with VAP[116,139] and one study investigated the pharmacokinetics of patients with cirrhosis[140]. In addition, one study investigated the pharmacokinetics of meropenem in patients with indwelling surgical drains[141] and two studies compared the pharmacokinetics of meropenem in obese patients and non-obese patients[131,142]. Fifteen studies investigated the pharmacokinetics of meropenem in patients with severe renal dysfunction[111,122,131,133,137,143–153] and in thirteen of these studies, patients were undergoing different types of hemodialysis[111,122,131,133,143–149,151–153].

The administered dose of meropenem differed much between and within the studies. While some patients were treated with 500 mg meropenem once daily, others received up to 2000 mg meropenem three times daily. This difference is explained to some extend by the fact that patients with all degrees of renal function were included in the different studies. Noticeably, the renal function, together with the site of infection are the only parameter used in the prescribing information for dose adjustment in adults[108]. Meropenem was administered intravenously as short infusion (about 10 to 30 min) or bolus injection in most studies. However, five studies investigated the effect of prolonged infusion[116,138,139,154,155] and six studies the effect of continuous infusion on the pharmacokinetics of meropenem[109,111,133,135,147,156].

Due to the different administration settings of meropenem and the different clinical situations of the patients, the resulting pharmacokinetic parameters and plasma levels of meropenem varied significantly between the different studies (see Table 4-1). The mean terminal half-life of meropenem in the different studies ranged from 1.0 hour[139] to 8.7 hours[153]. Noticeably, the mean terminal half-life was > 3.5 hours in all studies on patients with severe renal impairment. With the exception of the studies reported by Karjagin et al.[120] and Lheureux et al.[140], all studies without the criteria of impaired renal function showed terminal half-life < 3.5 hours. A possible explanation for the long terminal half-life reported in these studies might be the clinical situation of the patients (severe peritonitis associated with septic shock[120] and cirrhosis[140]). In addition, the renal function, expressed as creatinine clearance was highly variable in the study reported by Karjagin et al.[120] (52 ± 51 mL/min).

As one could expect, the clearance of meropenem also showed a large variability between the different studies. The reported meropenem clearance was ≤ 6 L/h in studies, which included patients with renal failure or severe renal dysfunction. The exception was one subgroup of patients in the study described by Isla et al.[145], which included exclusively patients receiving continuous venovenous hemodiafiltration (CVVHDF). Since meropenem clearance in this subgroup was 9.0 ± 4.6 L/h, and therefore significantly higher than in other patients receiving hemodialysis, this method seems to be very effective in the removal of meropenem from blood. The lowest value for meropenem clearance was found by Tegeder et al.[153] with a median of 3.1 L/h in patients undergoing CVVH and the highest was found by Isla et al.[145] with 63.9 ± 39.7

L/h in the subgroup of patients, who had creatinine clearance of 75 to 118 mL/min. Since this value is unlikely and several-fold as high as the resulting meropenem clearance in other subgroups in this study, it is unfortunate that the authors did ignore this issue in their discussion. In addition, the resulting volume of distribution of this subgroup was unlikely high with a value of 96.9 ± 66.6 L per 74 kg, which was the mean weight of patients in this subgroup. When excluding this study from analysis, the volume of distribution in all studies was in the range of 7.2 ± 1.8 L (mean ± SD) to 53.9 (IQR 32.9-78.4) per 70kg. This variability reflects the different clinical situations of the patients in the different studies as well as the large interindividual variability of this parameter in critically ill patients.

Overall, eighteen studies reported the area under the curve, which ranged from 67.6 to 388.6 µg*h/mL. Three studies reported AUC values < 100 µg*h/mL[71,109,137], after administration of 1000 mg of meropenem per dosing interval of eight hours. However, some of the patients in the study by Binder et al. might have received only 500 mg meropenem every 12 hours. With the exception of the study described by Novelli et al., which included patients with varying degrees of renal insufficiency, the patients of these studies had normal to slightly impaired renal function. Five studies reported AUC values > 200 µg*h/mL with a maximum of 388.6 µg*h/mL[133,139,150,151,154]. This high value might be explained by the high dose of 2000 mg meropenem every 8 hours. The remaining studies reported AUC values of 100 to 200 µg*h/mL.

In addition, the trough plasma levels of meropenem varied widely between and within the studies, reflecting the differing interindividual pharmacokinetic parameters and the different study settings (see Figure 4-2).

With the exception of five studies[109,135,137,139,145] all studies reached mean/median trough levels of 2 µg/mL, corresponding to the MIC breakpoint for common bacteria in critically ill patients as pseudomonas spp. and enterobacteriaceae[77]. However, due to the large interindividual variability, a number of patients failed to reach this PK/PD target.

Table 4-1 Pharmacokinetics of meropenem in critically ill patients.

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Zhao et al. 2017[135]	-	continuous infusion	25	Age: 68 ± 15 years APACHE II score: 19 ± 5 Weight: 61 ± 10 kg CLCR: 98 ± 43 mL/min	3000 /24h	i.v. continuous infusion	-	-	-	-
		intermittent infusion	25	Age: 67 ± 12 years APACHE II score: 20 ± 6 Weight: 64 ± 12 kg CLCR: 91 ± 34 mL/min	1000 q8h	i.v. infusion (30min)	-	-	13.8 ± 6.0	27.3 ± 4.8
Tsai et al. 2016[134]	-	Australian Indigenous	6	Age: 45 years [22-76] [a] SOFA score: 11 [10-15] [a] Weight: 73 kg [60-104] [a] CLCR: 98 mL/min [16-164] [a]	-	i.v. infusion (30min)	-	-	11.0 [3.0-14.1] [a]	V_1: 11.0 (9.8-17.0)
		Caucasian	5	Age: 55 years [29-69] [a] SOFA score: 3 [2-11] [a] Weight: 80 kg [60-110] [a] CLCR: 106 mL/min [20-144] [a]			-	-	17.4 [4.3-30.3] [a]	V_1:15.3 (9.7-18.4)
Mattioli et al. 2016[155]	-	-	27	Age: 62 ± 12 years APACHE II score: 13 ± 6 Weight: 76 ± 30 kg CLCR: 87 ± 44 mL/min	1000 or 2000 q8h or q12h	i.v. infusion (3h)	2.2 ± 1.5	-	9.4 ± 4.5	26.2 ± 14.6
Petersson et al. 2016[157]	-	-	19	Age: 64 years (IQR 50-73) [a] Weight: 80 kg (IQR 69-85) [a] CLCR: 101 mL/min (IQR 73-120) [a]	500 or 1000 q6h or q8h or q12h	-	2.0 (IQR 1.6-2.7)	-	-	-

If not indicated otherwise, data is presented as mean ± SD. Range is given in brackets; [a] Data is presented as median values; V_1: volume of distribution in the central compartment

Table 4-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Lheureux et al. 2016[140]	-	cirrhosis	38	Age: 56 years (IQR 46-59) [a] APACHE II score: 24 ± 5 Weight: 70 kg (IQR 60-81) [a] CLCR: 52 mL/min (IQR 36-60) [a,g]	total daily dose: 3000 (IQR 2000-3000)	-	4.9 (IQR 3.4-5.9)	-	5.8 (IQR 3.5-8.5)	30.1 (IQR 25.9-56) /70kg
		without cirrhosis	38	Age: 62 years (IQR 54-68) [a] APACHE II score: 20 ± 6 Weight: 70 kg (IQR 60-81) [a] CLCR: 47 mL/min (IQR 29-87) [a,g]			4.3 (IQR 3.3-6.6)	-	6.1 (IQR 3.6-16.7)	53.9 (IQR 32.9-78.4) /70kg
Alobaid et al. 2016[142]	-	obese	134	Age: 65 years (IQR 51-74) Weight: 100 kg (IQR 90-115) CLCR: 73 mL/min (IQR 42-124)	total daily dose: 3000 (IQR 2000-3000)	intermittent bolus or prolonged infusion	-	-	-	-
		non-obese	347	Age: 68 years (IQR 53-76) Weight: 73 kg (IQR 65-80) CLCR: 59 mL/min (IQR 34-99)			-	-	-	-
Jamal et al. 2015[133]	under-going CVVH	continuous infusion	8	Age: 48 years (32-63) [a] APACHE II score: 30 (IQR 27-33) [a] Weight: 80 kg (IQR 69-80) [a] CLCR: -	3000 /24h	i.v. continuous infusion	-	215.3 (IQR 196.0-250.4) [a]	4.6 (IQR 4.1-4.8) /80kg [a]	-
		intermittent bolus	8	Age: 45 years (29-61) [a] APACHE II score: 33 (IQR 30-38) [a] Weight: 60 kg (IQR 50-64) [a] CLCR: -	1000 q8h	i.v. infusion (30min)	4.4 (IQR 4.1-5.1)[a]	250.8 (IQR 215.5-294.8) [a]	4.1 (IQR 3.2-5.8) /60kg [a]	25.8 (IQR 24-30) /60kg [a]

If not indicated otherwise, data is presented as mean ± SD. [a] Data is presented as median values; [g] CLCR of patients receiving CRRT is not included

Table 4-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Jaruratanasirikul et al. 2015[136]	-	-	9	Age: 57 ± 16 APACHE II score: 22 ± 6 Weight: 63 ± 12kg CLCR: 79 ± 63 mL/min	1000 q8h	i.v. infusion (60min)	2.5 (RSE: 68.1%)	-	7.8 (RSE: 22.1%)	23.7 (RSE: 12.6%)
Langan et al. 2014[154]	-	Group1: 1000mg, 0.5h infusion	10 [b]	Age: 67 years (20-75) [a] APACHE II score: 23 (11-40) [a] Weight: 76 kg (50-113) [a] CLCR: Group1: 77 mL/min (IQR 47-108) [a]; Group2: 76 mL/min (IQR 65-90) [a]	1000 q8h or q12h	i.v. infusion (30min)	2.7 (IQR 1.4-3.7)[a]	207.7 (IQR 65.8-276.9) [a]	4.8 (IQR 3.6-15.2) [a]	18.9 (IQR 15.3-25.4) [a]
		Group2: 500mg, 3h infusion			500 q8h or q12h	i.v. infusion (3h)	2.6 (IQR 1.5-4.1)[a]	118.4 (IQR 40.8-149.2) [a]	4.2 (IQR 3.4-12.3) [a]	20.4 (IQR 17.9-25.7) [a]
Goncalves-Pereira et al. 2014[158]	-	initial PK parameters	15	Age: 73 years (IQR 21) [a] SOFA score: 4 (IQR 2.5) [a] Weight: 78 kg (IQR 12.5) [a] CLCR: 75 mL/min (IQR 33-145) [a]	1000 q8h	i.v. infusion (30min)	1.8-3.1	138.4-261.4	4.4 (2.7-7.2) [c]	Vss: 12.7-19.4
		initial PK parameters	7 [d]	CLCR: 66.7 mL/min (IQR 31.7) [a] SOFA score: 6 (IQR 3.5) [a]			-	-	7.2 (4.5-11.3) [d]	Vss: 18.5 (13.0-26.4) [d]
		late PK parameters		CLCR: 106.7 mL/min (IQR 46.7) [a] SOFA score: 3 (IQR 1) [a]			-	-	8.1 (4.4-13.7) [d]	Vss: 17.3 (7.3-41.0) [d]

If not indicated otherwise, data is presented as mean ± SD. Range is given in brackets; Vss: steady state volume of distribution; [a] Data is presented as median values; [b] crossover study design; [c] 95% confidence interval of the mean; [d] only 7 patients completed PK assessment for comparison with late PK parameters; [f] data of subgroups who were treated with other substances than meropenem or who are not critically ill is not shown

Table 4-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Binder et al. 2013[137]	hemato-logic / oncologic patients	neutropenic	6	Age: 52 years (35-75) APACHE II score: - Weight: 72 kg (48-85) CLCR: 89 mL/min (56-127)	1000 mg q8h	i.v. infusion (10-32min)	1.1 (0.8-1.4)	68.4 (48.3-95.5)	15.3 (10.5-20.7)	Vss: 19.3 (15-27.3)
		non-neutropenic	4				3.2 (2.1-4.8)	104.3 (93.4-120.3)	9.7 (8.3-10.7)	Vss: 29.3 (21.1-37.0)
	ICU patients	without renal impairment	6	Age: 53 years (42-70) APACHE II score: - Weight: 88 kg (72-129) CLCR: 81 mL/min (63-114)	500 or 1000 q8h or q12h	i.v. infusion (10-79min)	2.2 (0.8-3.2)	68.5 (18.2-156.4)	13.5 (5.9-23.9)	Vss: 33.6 (19.5-69.4)
		renal impairment	9	Age: 60 years (33-85) APACHE II score: - Weight: 78 kg (45-95) CLCR: 37 mL/min (10-56)			5.0 (3.3-7.2)	160.5 (48.9-327.8)	5.8 (1.8-9.4)	Vss: 34.5 (17.5-52.2)
Dulhunty et al. 2013[111]	severe sepsis	continuous infusion	10 [f]	Age: 54 ± 19 years APACHE II score: 21 ± 9 Weight: - Renal function: not undergoing CRRT	3000 /24h	i.v. continuous infusion	-	-	-	-
		intermittent infusion	12 [f]	Age: 60 ± 19 years APACHE II score: 23 ± 8 Weight: - Renal function: not undergoing CRRT	1000 q8h	i.v. bolus				
Adnan et al. 2013[141] [e]	with indwelling surgical drains	-	5 [f]	Age: 69 ± 15 years APACHE II score: 11 ± 2 Weight: 75 ± 23 kg SCr < 170µg/L	1000 q8h	i.v. infusion (30min)	3.2 (3.1-4.7)	128.7 (95.3-176.7)	5.7 (5.1-10.6)	30.8 (26.3-42.0) /75kg

If not indicated otherwise, data is presented as mean ± SD. Range is given in brackets; Vss: steady state volume of distribution; [e] no information if PK results are median or mean values; [f] data of subgroups who were treated with other substances than meropenem or who are not critically ill is not shown

Table 4-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Hites et al. 2013[131]	-	obese, with CRRT	37 [f] sample series	Age: 59 years (24-79) [a] APACHE II score: 18 (8-32) [a] Weight: 116 kg (80-178) [a] BMI: 40 kg/m^2 (30-60) [a] Renal function: 14 of 49 patients had SCr > 2.5mg/dL	3000 /24h	i.v. infusion (30min)	5.5 (2.3-115.5) [a]	-	4.5 (0.4-11.3) [a]	40.0 (8.0-191.0) [a]
		obese, without CRRT					1.6 (1.3-57.8) [a]		10.1 (1.6-29.3) [a]	
		non-obese, with CRRT	37 [f] sample series	Age: 57 years (19-91) [a] APACHE II score: 18 (8-36) [a] Weight: 61 kg (37-80) [a] BMI: 22 kg/m^2 (15-25) [a] Renal function: 9 of 59 patients had SCr > 2.5mg/dL			4.8 (2.0-15.1) [a]	-	3.7 (2.3-23.4) [a]	27.9 (5.4-205.2) [a]
		non-obese, without CRRT					1.3 (1.0-8.3) [a]		6.1 (2.1-16.5) [a]	
Seyler et al. 2011[143]	under-going CRRT	-	17 [f]	Age: 62 ± 16 years APACHE II score: 23 ± 8 Weight: - BMI: 26 ± 8 kg/m^2 Renal function: CRRT	1000 q12h	i.v. infusion (30min)	4.4 [a] (2.6-30.5)	134 [a] (61-291)	4.83 /70kg (2.268-14.154) [a]	31.5 /70kg (14.0-212.1) [a]
Jaruratanasirikul et al. 2011[138]	febrile neutropenic with bacteremia	1g, 10min infusion	8 [b]	Age: 43 ± 21 years APACHE II score: - Weight: 51 ± 18 kg CLCR: >60 mL/min	1000	i.v. infusion (10min)	-	-	6.3 ± 1.7	7.2 ± 1.8 /60kg
		1g, 3h infusion			1000	i.v. infusion (3h)				
		2g, 3h infusion			2000	i.v. infusion (3h)				
Lodise et al. 2011[116]	VAP	-	39	Age: 49 ± 19 years APACHE II score: - Weight: - CLCR: -	500 or 1000 or 2000 mg q8h	i.v. infusion (30min or 3h)	-	150.8 ± 87.4	15.2 ± 9.7	V_1: 12.6 ± 13.3

[a] Data is presented as median values; [b] crossover study design; [f] data of subgroups who were treated with other substances than meropenem or who are not critically ill is not shown; V_1: volume of distribution in the central compartment

Table 4-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Tacconne et al. 2010[132]	severe sepsis or septic shock	-	16 [f]	Age: 63 ± 13 years APACHE II score: 22 (IQR 18-28) [a, f] Weight: - BMI: 25 ± 5 kg/m^2 CLCR: 64 mL/min (22-134) [a]	1000 mg q8h to 500 mg q24h	i.v. infusion (30min)	2.1 (1.7-3.4) [a]	132 (91-179) [a]	7.9 (5.2-11.0)[a]	30.1 /70kg (21.7-53.9) [a]
Desh-pande et al. 2010[122]	under-going sustained low-efficiency dialysis	-	10	Age: 64 ± 12 years APACHE II score: - Weight: 89 ± 22 kg BMI: 36 ± 12 kg/m^2 Renal function: CRRT	1000 q12h	i.v. infusion (30min)	-	-	-	-
Bilgrami et al. 2010[144]	under-going high-volume CVVH	-	10	Age: 57 years (IQR 49-61) [a] APACHE II score: 25 (IQR 22-28) [a] Weight: 70 kg (IQR 66-103)[a] Renal function: CRRT	1000 q8h	i.v. bolus	4.3 (IQR 2.9-6.0)[a]	166.5 (IQR 160.5-193.1) [a]	6.0 (IQR 5.2-6.2) [a]	25.9 (IQR 22.4-32.2) [a]
Roberts et al. 2009[109]	without renal dys-function	intermittent infusion	5	Age: 55 years (IQR 48-61) [a] APACHE II score: - Weight: 80 kg (IQR 75-85) [a] CLCR: 106 mL/min (IQR 98-127) [a]	1000 q8h	i.v. bolus (3min)	-	69.1 [a]	-	-
		continuous infusion	5	Age: 57 years (IQR 54-63) [a] APACHE II score: - Weight: 75 kg (IQR 75-85) [a] CLCR: 93 mL/min (IQR 69-161) [a]	3000 /24h	i.v. continuous infusion		67.6 [a]		

[a] Data is presented as median values; [f] data of subgroups who were treated with other substances than meropenem or who are not critically ill is not shown

Table 4-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Isla et al. 2008[146]	undergoing CRRT	septic patients	13	Age: 69 ± 12 years APACHE II score: 18 ± 6 Weight: 72 ± 7 kg Renal function: CRRT	500 or 1000 or 2000 mg q6h or q8h	i.v. infusion (< 20min)	-	-	6.63+0.064x CLCR	V_1: 15.7 ± 10% CV
		polytrauma-tized patients	7	Age: 33 ± 10 years APACHE II score: 23 ± 7 Weight: 76 ± 6 kg Renal function: CRRT					6.63+0.72x CLCR	V_1: 69.5 ± 18% CV
Lang-gartner et al. 2008[147]	undergoing CVVHD	intermittent infusion	6 [b]	Age: 54 ± 8 years APACHE II score: - Weight: 76 ± 17 kg Renal function: CRRT	1000 q12h	i.v. infusion (15-20min)	5.3 (IQR 5.1-7.0)[a]	-	4.3 (IQR 3.9-5.0) [a]	32.3 (IQR 28.9-40.7) [a]
		continuous infusion			2000 /24h	i.v. continuous infusion	-		4.40 (IQR 3.58-5.58) [a]	-
Karjagin et al. 2008[120]	severe peritonitis with septic shock	-	6	Age: 66 ± 11 years APACHE II score: 17 ± 9 Weight: 70 ± 17 kg CLCR: 52 ± 51 mL/min	1000 q8h	i.v. infusion (20min)	3.7 ± 2.0	-	6.7 ± 4.2	Vss: 23.8 ± 4.9

[a] Data is presented as median values; [b] crossover study design; V_1: volume of distribution in the central compartment; Vss: steady state volume of distribution

Table 4-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Isla et al. 2005[145]	undergoing CRRT	CLCR 0-5 mL/min	7	Age: 65 ± 15 years APACHE II score: 19 ± 7 Weight: 76 ± 4 kg CLCR: 1 ± 2 mL/min	500 q6h or q8h or 1000 q8h	i.v. infusion (20min)	3.7 ± 0.8	-	9.0 ± 4.6	Vss: 43.3 ± 22.0 /76kg
		CLCR 10-45 mL/min	7	Age: 66 ± 15 years APACHE II score: 16 ± 6 Weight: 69 ± 8 kg CLCR: 23 ± 14 mL/min	500 q6h or 1000 q8h		2.7 ± 0.7		8.1 ± 3.4	Vss: 25.5 ± 6.9 /69kg
		CLCR 75-118 mL/min	6	Age: 35 ± 18 years APACHE II score: 23 ± 6 Weight: 74 ± 4 kg CLCR: 76 ± 19 mL/min	1000 q6h or 2000 q8h		1.5 ± 0.5		63.9 ± 39.7	Vss: 96.9 ± 66.6 /74kg
Jaruratanasirikul et al. 2005[139]	VAP	1g, bolus	9 [b]	Age: 40 ± 16 years APACHE II score: - Weight: 54 ± 12 kg CLCR: >60 mL/min	1000 q8h	i.v. bolus	1.4 ± 0.6	136.3 ± 58.5	8.5 ± 3.2	16.0 ± 3.7
		1g, 3h infusion			1000 q8h	i.v. infusion (3h)	1.0 ± 0.3	186.2 ± 79.5	6.4 ± 2.8	9.3 ± 4.9
		2g, 3h infusion			2000 q8h		1.2 ± 0.4	388.6 ± 220.0	7.2 ± 4.8	11.9 ± 7.9
Novelli et al. 2005[71]	sepsis	-	10 [f]	Age: 67 years ± 19 APACHE II score: - Weight: 72 kg ± 15 CLCR: 61 mL/min ± 38	1000	i.v. infusion (30min)	2.1 ± 0.6	99.5 ± 23.9	11.5 ± 3.1	27.1 ± 7.7
Krueger et al. 2003[148]	acute renal failure, undergoing CRRT	-	8	Age: 67 ± 9 years APACHE II score: 30 ± 7 Weight: 80 ± 15 kg Renal function: CRRT	500 q12h	i.v. infusion (30min)	3.6 ± 0.8	105.3 ± 21.7	5.0 ± 1.3	Vss: 22.4 ± 5.6 /80kg
Robatel et al. 2003[149]	undergoing CRRT	-	15	Age: 61 ± 8 years APACHE II score: - Weight: 71 ± 16 kg CLCR: 33 ± 12 mL/min	500 q8h or q12h or 1000 q12h	i.v. infusion (25min)	5.1 ± 35%	-	4.5 ± 41%	33.2 ± 28%

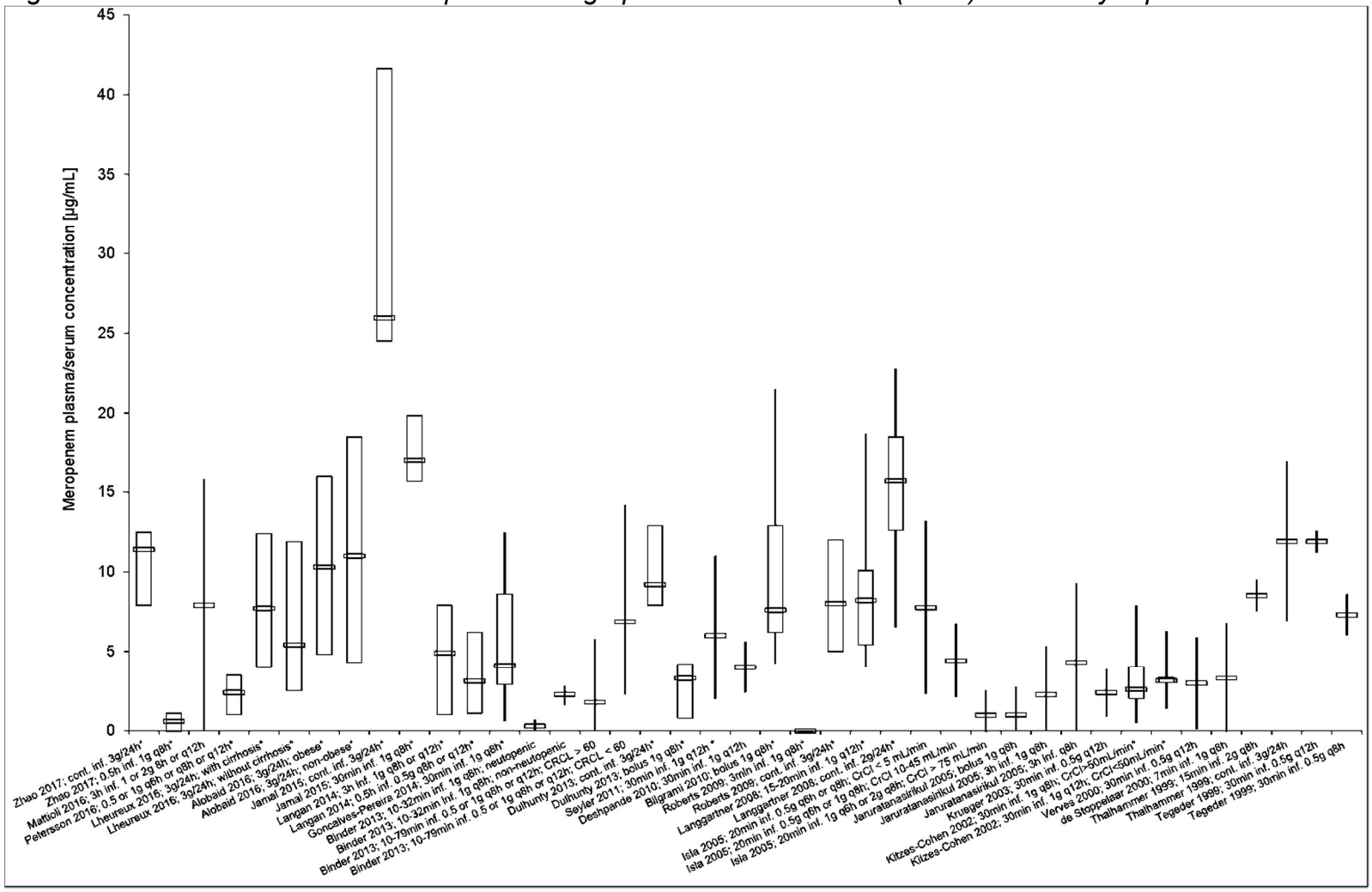
[b] crossover study design; f data of subgroups who were treated with other substances than meropenem or who are not critically ill is not shown

Table 4-1 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of patients	Patient demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Kitzes-Cohen et al. 2002[150]	-	CLCR > 50 mL/min	8	Age: 74 ± 10 years APACHE II score: - Weight: - CLCR: 71 ± 15 mL/min	1000 q8h	i.v. infusion (30min)	2.5 ± 1.2	119.4 ± 32.6	9.4 ± 2.4	Vss: 21.7 ± 5.7
		CLCR < 50 mL/min	7	Age: 73 ± 6 years APACHE II score: - Weight: - CLCR: 36 ± 9 mL/min	1000 q12h		3.9 ± 1.6	230.2 ± 43.3	4.7 ± 1.0	Vss: 17.1 ± 2.1
Giles et al. 2000[151]	under-going CRRT	-	10	Age: 65 ± 8 years APACHE II score: 27 ± 6 Weight: 80 ± 19 kg Renal function: CRRT	1000 q12h	i.v. infusion (5min)	5.2 ± 1.8	246.0 ± 97.1	4.3 ± 1.4	Vss: 27.3 ± 9.8
Ververs et al. 2000[152]	under-going CRRT	-	5	Age: 47 ± 13 years APACHE II score: - Weight: 86 ± 12 kg Renal function: CRRT	500 q12h	i.v. infusion (30min)	6.4 ± 2.0	129.5 ± 26.4	4.6 ± 0.9	31.8 ± 12.9 /86kg
de Stoppelaar et al. 2000[159]	VAP	-	8	Age: 55 ± 8 years APACHE II score: - Weight: 73 ± 11 kg CLCR: 85 ± 26 mL/min	1000 q8h	i.v. infusion (7min)	3.1 ± 1.7	102.7 ± 42.9	11.0 ± 4.3	Vss: 34.4 ± 15.9
Thalhammer et al. 1999[156]	-	intermittent infusion	15 [b]	Age: 55 ± 14 years APACHE II score: - Weight: 84 ± 15 kg CLCR: 84 ± 53 mL/min	2000 q8h	i.v. infusion (15min)	2.4 ± 0.7	193.8 ± 21.1	9.4 ± 1.2	Vss: 26.6 ± 3.2
		continuous infusion			3000 /24h	i.v. continuous infusion	-	117.5 ± 12.9	7.7 ± 1.4	Vss: 25.9 ± 5.7
Tegeder et al. 1999[153]	under-going CVVH	q8h	5	Age: 66 ± 13 years APACHE II score: - Weight: - CLCR: 1 ± 2 mL/min	500 q8h	i.v. infusion (30min)	8.7 ± 3.5	-	3.1 ± 0.5	Vss: 12.4 ± 1.8

[b] crossover study design; Vss: steady state volume of distribution

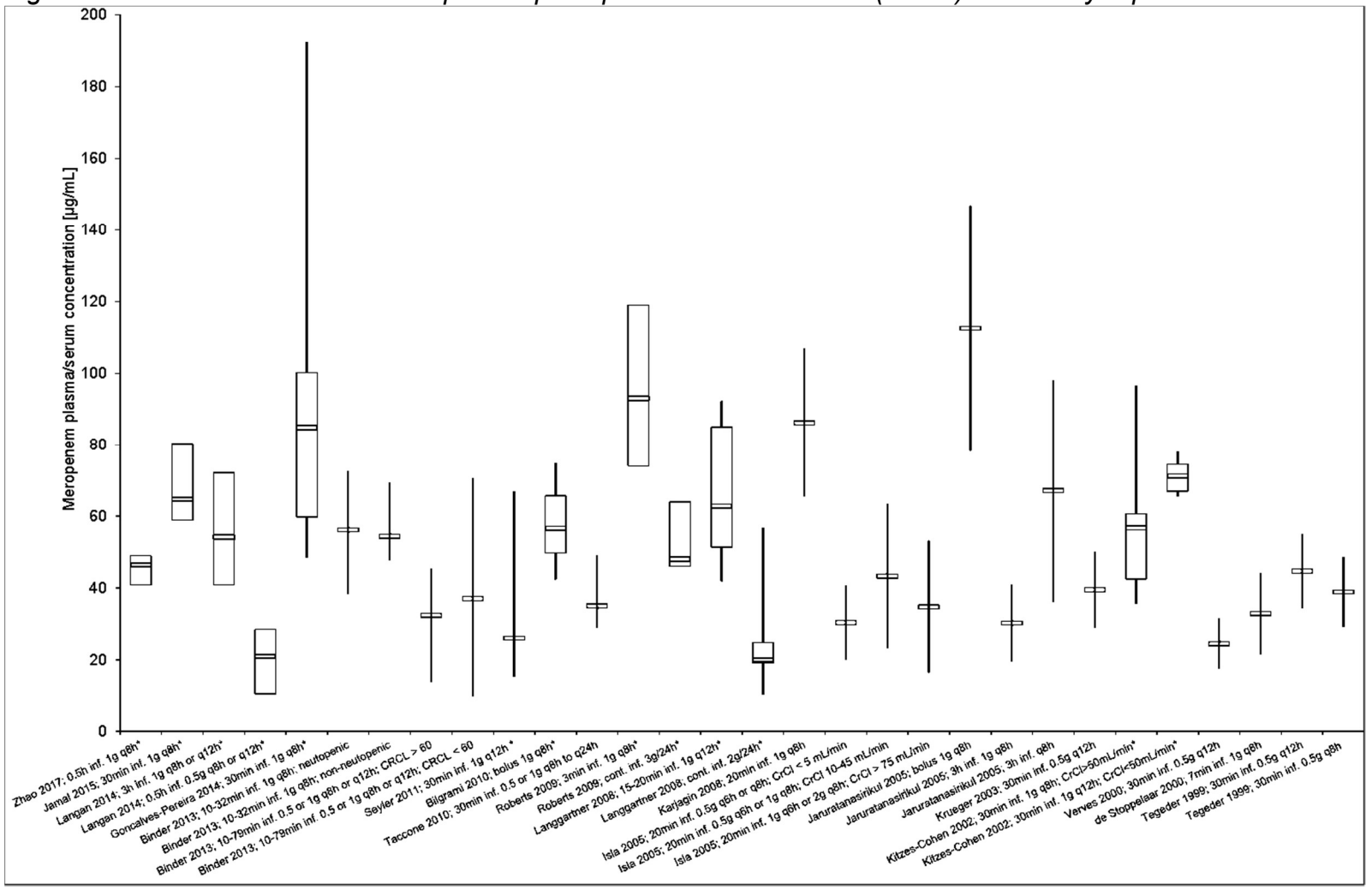
Figure 4-2 Literature data of meropenem trough plasma / serum levels (Cmin) in critically ill patients.



If not indicated otherwise, data is shown as the mean ± SD.

* Data is presented as the median (dash), the minimum and maximum range (whisker) and with or without the IQR (box)

Figure 4-3 Literature data of meropenem peak plasma / serum levels (Cmax) in critically ill patients.



If not indicated otherwise, data is shown as the mean ± SD.

* Data is presented as the median (dash), the minimum and maximum range (whisker) and with or without the IQR (box)

4.3.3. Pharmacokinetics of meropenem in healthy volunteers

Sixteen studies on the pharmacokinetics of meropenem in healthy volunteers were included in this overview. The most recent paper was from 2015, the oldest ones date back to 1991. The number of participants was in the range of five to twenty-six.

An overview of these studies and the resulting pharmacokinetic parameters is provided in Table 4-2. The trough and peak plasma concentrations of meropenem from the different studies are compared and illustrated in Figure 4-4 and 4-5.

All studies included in this overview investigated the pharmacokinetics of meropenem in healthy volunteers. However, a number of studies focused on factors influencing the pharmacokinetics of meropenem. Lee et al.[79] and Jaruratanasirikul et al.[160] studied the influence of prolonged and Krueger et al.[161] and Mouton et al.[162] of continuous infusions on the pharmacokinetics of meropenem. In contrast to the other studies, which included healthy volunteers of younger age, Ljungberg et al.[163] compared the pharmacokinetics of meropenem in young vs. elderly healthy volunteers. While most studies in healthy volunteers investigated single dose pharmacokinetics of meropenem, some also investigated the pharmacokinetics of meropenem after multiple dose treatment or during continuous infusion[117,161,162,164]. The intermittent dosages of meropenem in the different studies were in the range of 500 to 2000 mg either administered as single dose or multiple dose. With the exception of the study reported by Mouton et al.[162], in which 10 mg/kg meropenem were administered four times daily, meropenem was administered three times daily in all multiple dose regimens. Two studies[161,162] administered meropenem as continuous infusion with dosages of either 1500 or 3000 mg/24h or 30 mg/kg/18h.

The reported mean ± SD half-life of meropenem was in the range of 0.8 to 1.2 hours except of one study. In this study[160], a quite short half-life for meropenem of 0.5 and 0.6 hours was reported after prolonged infusion of 500 and 1000 mg of meropenem, respectively. In the third treatment arm of this crossover study, meropenem was administered as intravenous bolus injection and the resulting mean half-life in this treatment arm was 1.1 hours. Therefore, a possible reason for the unlikely short half-life of meropenem in the two treatment arms receiving prolonged infusions of meropenem might be the inclusion of PK samples in the analysis, which were not in the terminal phase of elimination. This might also explain the low volume

of distribution of 9.8 ± 0.6 and 11.9 ± 0.4 L in these two subgroups, in which meropenem was administered as prolonged infusion. Two studies used compartmental analysis for the determination of the pharmacokinetic parameters of meropenem and provided only values of the volume of distribution in the central compartment (V_1)[79,161]. The resulting mean V_1 of these studies was in the range of 6.8 to 12.4 L. If these results were excluded from analysis, the mean volume of distribution of meropenem in the remaining studies was in the range of 11.7 to 26.1 L.

The reported mean clearance of meropenem was in the range of 8.3 to 20.3 L/h. As might be expected the lowest meropenem clearance of 8.3 ± 1.2 L/h resulted in the subgroup of elderly healthy volunteers, described in the study of Ljungberg et al.[163].

The peak concentrations and the area under the curve of meropenem in healthy individuals were mainly dependent on the administered dose and the duration of the infusion. As a result, the highest peak concentration of µg*h/mL 131.7 µg/mL resulted after the administration of 2000 mg meropenem over 30 minutes three times daily[117]. The corresponding area under the curve of 156.7 µg*h/mL was also the second highest reported of all studies in healthy individuals included in this overview. Only one study [165], where 2000 mg meropenem were administered over three hours, reported a higher area under the curve of 186 ± 33.6 µg*h/mL. The corresponding peak concentration in this study was 58.2 ± 10.8 µg/mL. In the study reported by Dandekar et al.[164], the administration of the same dose, also over three hours resulted in a mean peak concentration of 39.8 µg/mL and an area under the curve of 126.7 µg*h/mL. The reported mean peak concentrations after the administration of 1000 mg of meropenem in studies on healthy volunteers were in the range of 24.95 µg/mL, resulting after prolonged infusion over three hours, to 118.6 µg/mL, resulting after bolus injection[160]. The corresponding area under the curve was 80.1 and 97.6 µg*h/mL, respectively. Noteworthy, this data emerged from different treatment arms of a crossover-design study. The administration of 500 mg of meropenem resulted in mean peak plasma concentration in the range of 9.71 µg/mL after prolonged infusion[164] to 52.2 µg/mL after short term infusion over five minutes[166]. The corresponding AUC was in the range of 27.2[167] to 58.3 µg*h/mL[163]. The latter resulted in the subgroup of elderly patients reported by Ljungberg et al.

Trough plasma levels of meropenem in studies on healthy volunteers were all < 1 µg/mL, except of one study[164]. In this study, volunteers were treated with a high dose of 2000 mg meropenem three times daily. The resulting mean trough concentration of meropenem in this study was 1.58 µg/mL. In addition, two studies reported the steady-state concentrations of meropenem during continuous infusion[161,162]. The administration of 1500 and 3000 mg meropenem per 24 hours resulted in a mean steady-state concentration of 4.34 and 7.58 µg/mL, respectively, and the administration of 30 mg/kg per 18 hours resulted in a mean steady-state concentration of 6.3 µg/mL.

Table 4-2 Pharmacokinetics of meropenem in healthy volunteers.

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of subjects	Subject demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Wenzler et al. 2015[165]	healthy volunteers	-	25	Age: 39 ± 11 years Weight: 80 ± 9 kg CLCR: 94 ± 23 mL/min	2000 q8h	i.v. infusion (3h)	1.0 ± 0.2	186 ± 33.6	11.1 ± 2.1	Vss: 16.3 ± 2.6
Lee et al. 2010[79]	healthy volunteers	0.5h infusion	18 [b]	Age: 38 ± 10 years Weight: 74 ± 9 kg	1000 (single dose)	i.v. infusion (30min)	-	72.8 ± 17.1	13.7 ± 3.2	V_1: 10.3 ± 3.0
		3h infusion				i.v. infusion (3h)	-	68.0 ± 15.8	14.7 ± 3.4	V_1: 6.8 ± 3.0
Leelarasamee et al. 2008[168]	healthy volunteers	generic	26 [b]	Age: 20 - 40 years Weight: -	1000 (single dose)	i.v. infusion (30min)	1.0 ± 0.1	62.8 ± 8.4	-	-
		original					1.0 ± 0.1	63.6 ± 11.0		
Conte et al. 2005[117]	healthy volunteers	0.5g	20	Age: 33 ± 7 years Weight: 68 ± 11 kg SCr: 0.9 ± 0.2 mg/dL	500 q8h	i.v. infusion (30min)	-	28.6	-	-
		1g	20	Age: 29 ± 6 years Weight: 72 ± 13 kg SCr: 0.9 ± 0.2 mg/dL	1000 q8h			55.5		
		2g	8	Age: 33 ± 7 years Weight: 72 ± 13 kg SCr: 1.0 ± 0.1 mg/dL	2000 q8h			156.7		

Data is presented as mean ± SD. Range is given in brackets.
[b] crossover study design; V_1: volume of distribution in the central compartment

Table 4-2 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of subjects	Subject demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Krueger et al. 2005[161]	healthy volunteers	low dose, intermittent infusion	8 [b]	Age: 21 ± 3 years Weight: 67 ± 14 kg	500 q8h	i.v. infusion (30min)	-	-	16.3 ± 3.1	V_1: 12.4 ± 3.5
		low dose, continuous infusion			1500 /24h	i.v. continuous infusion				
		high dose, intermittent infusion	8 [b]	Age: 24 ± 4 years Weight: 66 ± 12 kg	1000 q8h	i.v. infusion (30min)				
		high dose continuous infusion			3000 /24h	i.v. continuous infusion				
Dandekar et al. 2003[164]	healthy volunteers	0.5g	6 [b]	Age: 34 ± 12 years Weight: 82 ± 19 kg	500 q8h	i.v. infusion (3h)	0.9 ± 0.1	28.4 ± 2.9	15.6 ± 1.7	Vss: 21.2 ± 2.6
		2g			2000 q8h		1.0 ± 0.2	126.7 ± 28.8	15.2 ± 3.8	Vss: 22.3 ± 1.5
Jaruratanasirikul et al. 2003[160]	healthy volunteers	1g, bolus	12 [b]	Age: 33 ± 9 years Weight: 60 ± 8 kg	1000 (single dose)	i.v. bolus	1.1 ± 0.7	97.6 ± 20.1	10.3 ± 5.0	16.8 ± 5.1
		1g, 3h infusion			1000 (single dose)	i.v. infusion (3h)	0.6 ± 0.0	80.1 ± 21.9	13.0 ± 0.2	11.9 ± 0.4
		0.5g, 3h infusion			500 (single dose)	i.v. infusion (3h)	0.5 ± 0.0	42.9 ± 9.0	12.3 ± 0.3	9.8 ± 0.6

[b] crossover study design; Vss: steady state volume of distribution

Table 4-2 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of subjects	Subject demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Jones et al. 1997	healthy volunteers	2min infusion	9 [b]	Age: 37 years (23-59) Weight: 79 kg (68-90)	1000 (single dose)	i.v. infusion (2min infusion)	0.9 ± 0.1	65.3 ± 9.9	15.0 ± 2.5	16.7 ± 3.0
		3min infusion				i.v. infusion (3min infusion)	0.9 ± 0.1	67.7 ± 12.7	14.7 ± 2.6	16.6 ± 2.7
		5min infusion				i.v. infusion (5min infusion)	1.1 ± 0.1	68.2 ± 7.4	14.3 ± 1.6	16.6 ± 2.6
Dreetz et al. 1996[87]	healthy volunteers	-	12	Age: 29 ± 6 years Weight: 80 ± 7 kg CLCR: 112 ± 13 mL/min/1.73m^2	1000 (single dose)	i.v. infusion (30min)	1.1 ± 0.1	70.5 ± 10.3	14.4 ± 1.8 /1.73m^2	18.6 ± 3.0 /70kg
Kelly et al. 1995[166]	healthy volunteers	0.5g, 5min infusion	5	Age: 29 years (18-39) Weight: 82 kg (73-88)	500 (single dose)	i.v. infusion (5min infusion)	1.1 ± 0.1	32.6 ± 5.1	15.7 ± 2.5	Vss: 16.2 ± 1.6
		0.5g, 30min infusion				i.v. infusion (30min)	1.0 ± 0.2	28.1 ± 4.3	18.1 ± 2.7	Vss: 19.6 ± 5.3
		1g, 5min infusion	6	Age: 34 years (24-42) Weight: 75 kg (63-89)	1000 (single dose)	i.v. infusion (5min infusion)	1.0 ± 0.1	83.2 ± 14.7	12.6 ± 1.7	Vss: 15.7 ± 1.4
		1g, 30min infusion				i.v. infusion (30min)	1.0 ± 0.1	77.2 ± 11.8	13.4 ± 2.0	Vss: 16.9 ± 2.3
Leroy et al. 1992[124]	healthy volunteers	-	6 [f]	Age: 34 ± 9 years Weight: 67 ± 12 kg CLCR: 123 ± 14 mL/min	500 (single dose)	i.v. infusion (30min)	1.2 ± 0.2	28 ± 15	19.7 ± 5.7	Vss: 26.1 ± 6.7 /67kg
Christens-son et al. 1992[169]	healthy volunteers	-	6 [f,g]	Age: 34 ± 13 years Weight: 79 ± 8 kg CLCR: 99 ± 26 mL/min/1.73m^2	500 (single dose)	i.v. infusion (30min)	0.9	36.0 ± 4.5	11.2 ± 1.7 /1.73m^2	Vss: 16.6 ± 2.4 /79kg

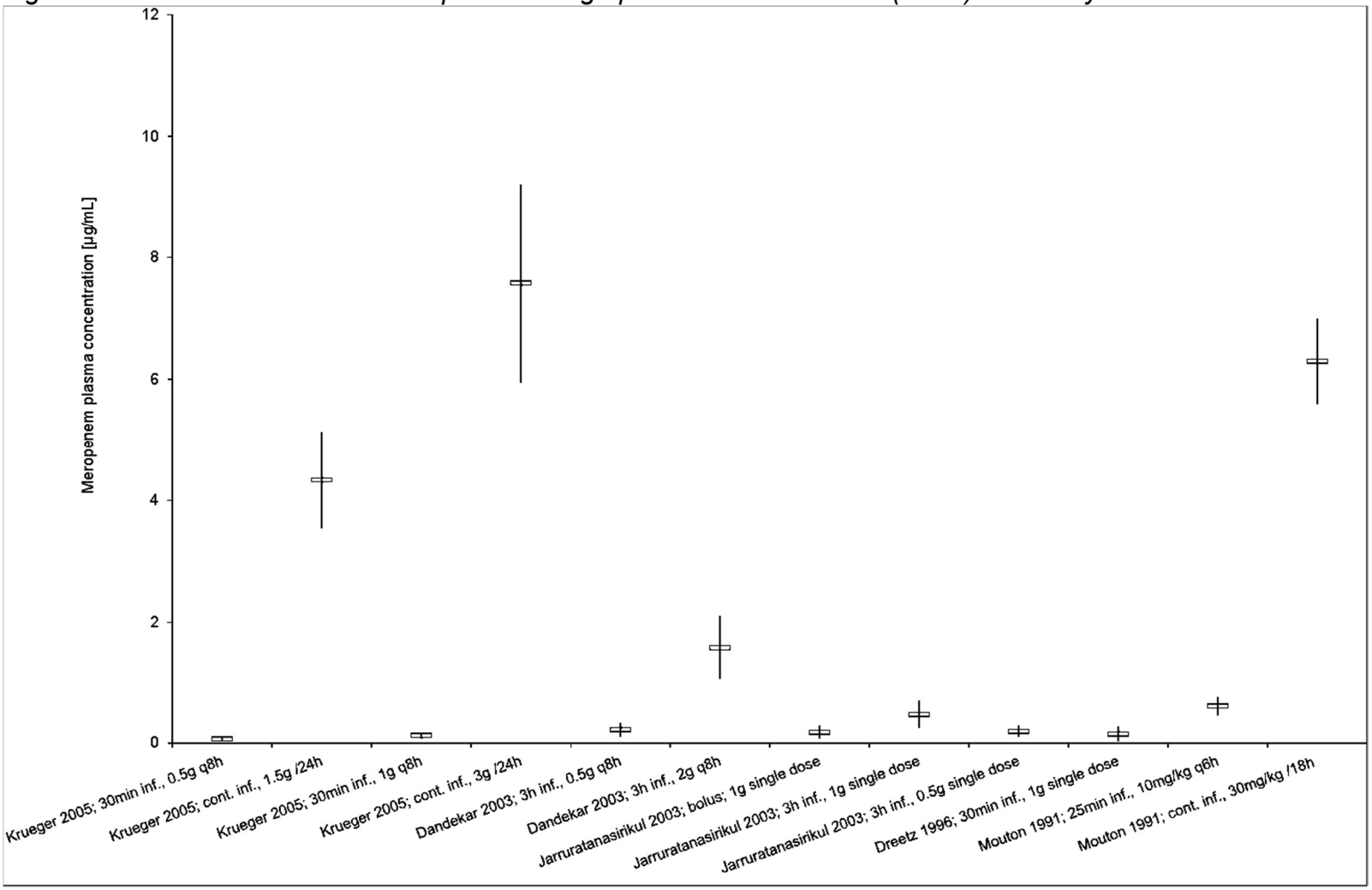
[b] crossover study design; [f] data of subgroups who were treated with other substances than meropenem or who are not healthy volunteers is not shown;
[g] one aubject with normal renal function was included; Vss: steady state volume of distribution

Table 4-2 continued

Reference	Study population				Drug administration		PK results			
	Clinical situation	Subgroups	No. of subjects	Subject demographics	Dosage MER [mg]	Administration route	$t_{1/2}$ [hours]	AUC [µg*h/mL]	CL [L/h]	Vd [L]
Ljungberg et al. 1992[163]	healthy volunteers	young	8	Age: 28 ± 5 years Weight: 69 ± 8 kg GFR [h]: 99 ± 7 mL/min/1.73m^2	500 (single dose)	i.v. infusion (30min)	0.8	39.6 ± 6.8	12.2 ± 1.7	Vss: 11.7 ± 1.2
		elderly	8	Age: 73 ± 5 years Weight: 69 ± 8 kg GFR [h]: 72 ± 12 mL/min/1.73m^2			1.3	58.3 ± 10.0	8.3 ± 1.2	Vss: 13.2 ± 1.4
Mouton et al. 1991[162]	healthy volunteers	intermittent infusion	8	Age: 24 ± 3 years Weight: 75 ± 8 kg	10mg/kg q6h	i.v. infusion (25min)	1.0 ± 0.2	43.5 ± 7.1	17.5 ± 2.2	Vss: 20.7 ± 2.7 /75kg
		continuous infusion			30mg/kg /18h	i.v. continuous infusion	-	-	20.3 ± 2.7	-
Burman et al. 1991[167]	healthy volunteers	-	6	Age: 35 years (30-40) Weight: 83 kg (68-93)	500 (single dose)	i.v. infusion (30min)	0.8 ± 0.0	27.2 ± 2.2	16.6 ± 0.6	Vss: 20.4 ± 0.7
Nilsson-Ehle et al. 1991[86]	healthy volunteers	-	8	Age: 33 years (22-38) Weight: 74 kg (66-86) CLCR: -	1000 (single dose)	i.v. infusion (30min)	1.0	77.5 ± 11.5	11.3 ± 1.95	Vss: 12.5 ± 1.5

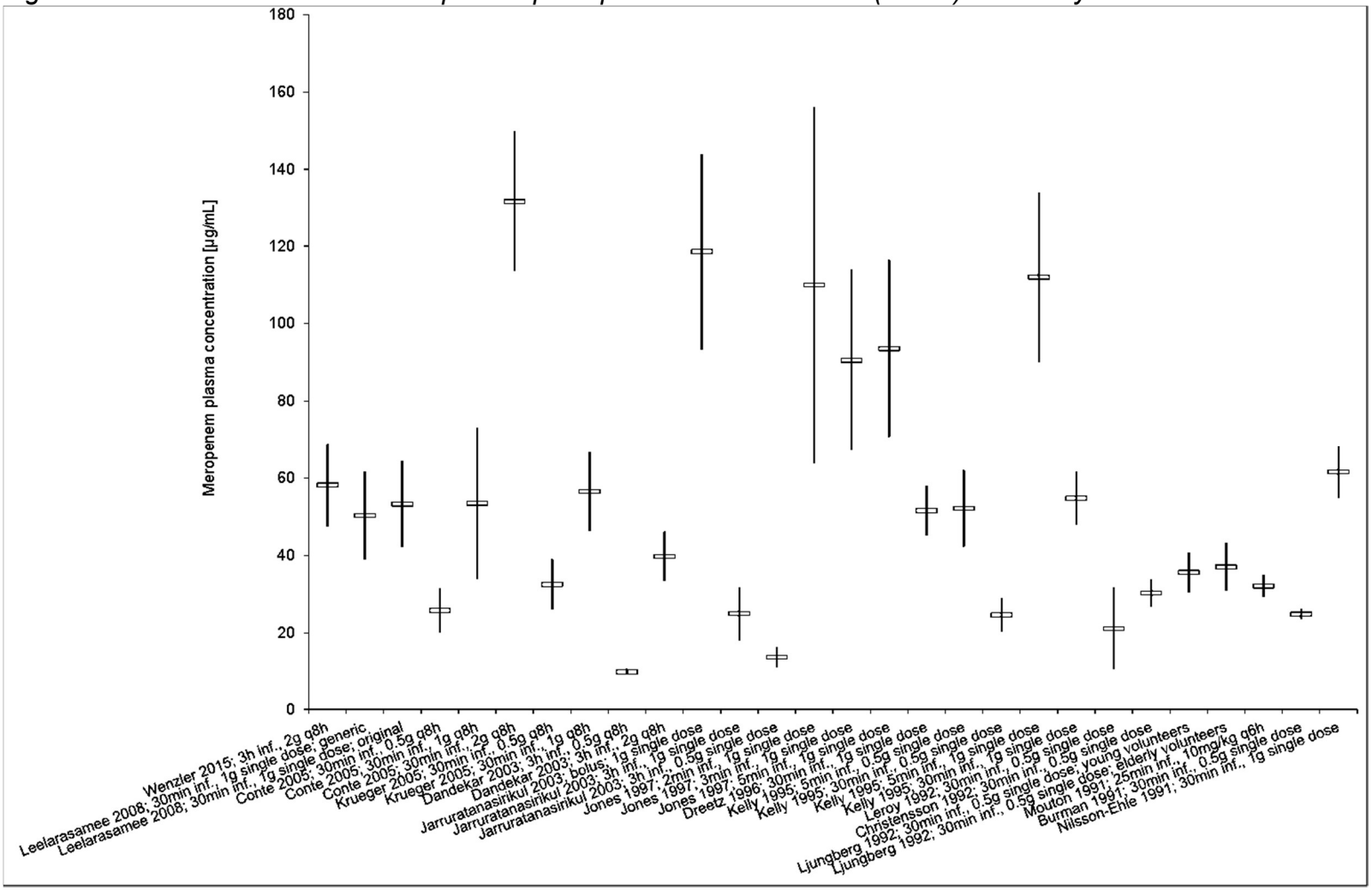
[h] Iohexol clearance; Vss: steady state volume of distribution

Figure 4-4 Literature data of meropenem trough plasma / serum levels (Cmin) in healthy volunteers.



Data is shown as the mean ± SD.

Figure 4-5 Literature data of meropenem peak plasma / serum levels (Cmax) in healthy volunteers.

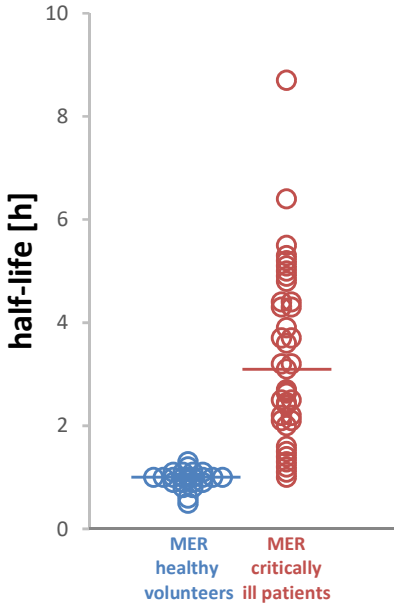


Data is shown as the mean ± SD.

4.3.4. Differences in the pharmacokinetics of meropenem in critically ill patients and healthy volunteers

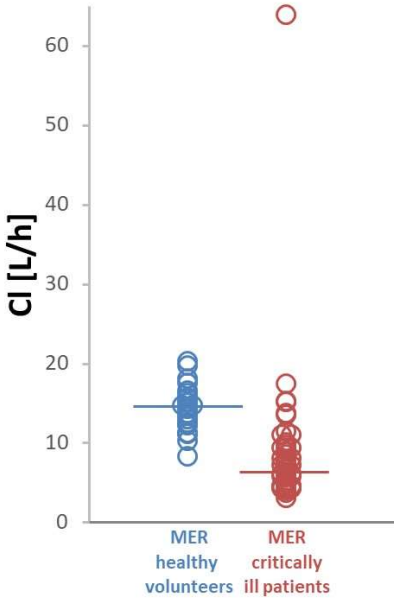
As shown in Figure 4-6 and 4-7, the median half-life of meropenem in studies on healthy volunteers was significantly below the median half-life resulting from studies in critically ill patients (1.0 vs. 3.1 h) and the median clearance of meropenem was significantly lower in critically ill patients than in healthy subjects (6.6 vs. 14.4 L/h). However, the reported half-life of meropenem in critically ill patients was much more variable compared to healthy individuals than the clearance.

Figure 4-6 Half-life of meropenem in healthy volunteers and critically ill patients.



The lines indicate the medians of all studies in one group, and each circle indicates the mean half-life of one study or one study-subgroup.

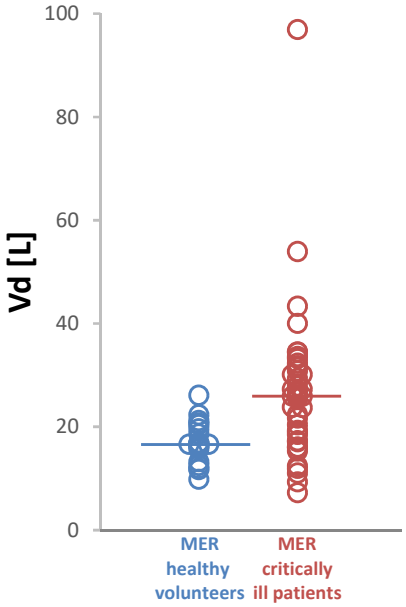
Figure 4-7 Clearance of meropenem in healthy volunteers and critically ill patients.



The lines indicate the medians of one group, and each circle indicates the mean clearance of one study or one study subgroup.

As shown in Figure 4-8, the volume of distribution of meropenem reported in critically ill patients was significantly larger than in healthy volunteers. While the median volume of distribution of meropenem was 16.6 L in studies on healthy volunteers, the resulting median volume of distribution in critically ill patients was almost twice as high (25.9 L).

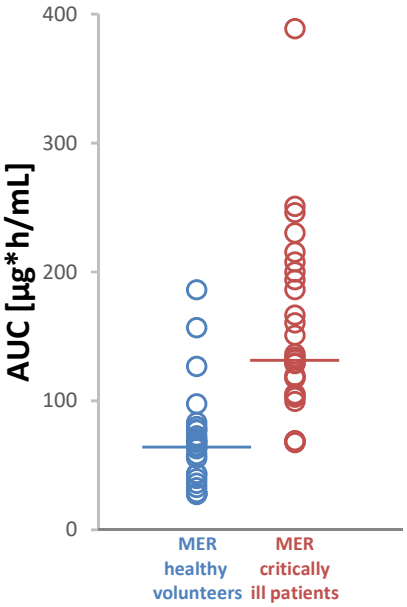
Figure 4-8 Volume of distribution of meropenem in healthy volunteers and critically ill patients.



The lines indicate the medians of one group, and each circle indicates the mean volume of distribution of one study or one study subgroup.

As shown in Figure 4-9, the median AUC of meropenem in critically ill patients was more than twice as high as the median AUC in healthy volunteers (64.5 vs. 133.0 µg*h/mL). However, this result is not astonishing, as critically ill patients received most often higher dosages and were dosed several times, while healthy volunteers received often only single-dose treatment. In addition, resulting from the data of half-life and clearance of meropenem in critically ill patents, the elimination of meropenem is significantly limited in a number of critically ill patients.

Figure 4-9 Area under the curve of meropenem in healthy volunteers and critically ill patients.



The lines indicate the medians of one group, and each circle indicates the mean area under the curve of one study or one study subgroup.

4.4. Conclusion

This retrospective data analysis provides an overview of the existing pharmacokinetic data of meropenem in critically ill patients and healthy volunteers. As pointed out, the pharmacokinetics of meropenem in critically ill patients varied substantially between and within the studies compared with healthy individuals.

As achieving and maintaining adequate plasma levels of antibiotics is highly important to the clinical course and survival of critically ill patients, this overview emphasizes the importance of monitoring the blood levels of meropenem in critically ill patients.

5. Individualizing meropenem prolonged infusions in intensive care unit patients via population modeling of renal function and infection biomarkers over time

5.1. Introduction

Meropenem is an important broad-spectrum antibiotic that is commonly used for empiric therapy of critically ill patients[44,170]. Due to its excellent safety profile, meropenem doses up to 6 g/day have been safely administered[171,172]. Several small pharmacokinetic (PK) studies (n=6 to 16 patients per study) showed that clearance and volume of distribution and consequently meropenem concentrations are highly variable in critically ill patients[44]. To optimize the pharmacodynamic (PD) profile of meropenem, some clinicians use prolonged or continuous infusions to increase the duration of unbound meropenem concentrations above the MIC ($fT_{>MIC}$) compared to the $fT_{>MIC}$ for short-term infusions[161].

Meropenem is predominantly eliminated renally and its doses are adjusted based on creatinine clearance and body weight[108,173]. However, this dose adjustment does not adequately capture patients with acute renal impairment or temporarily augmented renal function during sepsis or septic shock. When renal function changes rapidly in these patients, neither creatinine nor meropenem concentrations are at steady-state and thus renal function cannot be reliably calculated using the Cockcroft and Gault[96] and most other commonly used equations. For patients with unstable renal function, equations such as the Jelliffe & Jelliffe[174] or Chiou[175] methods are available but less commonly used. Currently, dosing of such critically ill patients with unstable PK is most commonly empiric and meropenem concentrations are not routinely measured for dose individualization via therapeutic drug management[114].

Our first objective was to implement a clinically-feasible dose individualization algorithm for meropenem in intensive care unit (ICU) patients with or without sepsis or septic shock. As second objective, we sought to characterize the population pharmacokinetics and change of renal function and infection biomarkers (C-reactive protein and procalcitonin) over time. Meropenem concentrations were measured in real-time for dose individualization. We developed a novel modeling approach that simultaneously fits the meropenem and serum creatinine concentrations to estimate the time-course of renal function (creatinine clearance).

In addition to the population pharmacokinetic analysis, a non-compartmental approach with the same data was performed to describe the pharmacokinetics of meropenem in a more simple way.

5.2. Methods

5.2.1. Study design and population

This prospective cohort study was carried out in the surgical intensive care unit of the Paracelsus Medical University, Nürnberg, Germany, from January to October 2014. Eligibility criteria were age ≥18 years, provision of informed consent, and the diagnosis of abdominal infection (peritonitis, organ infection) or pneumonia. This study included patients with or without sepsis, severe sepsis or septic shock who were treated with meropenem. Exclusion criteria were severe anemia or known allergy to meropenem. The study was approved by the local Ethics Committee and is registered in the United States National Library of Medicine (no. NCT01702545) and the German Register of Clinical Trials („Deutsches Register Klinischer Studien“; no. DRKS00004392).

5.2.2. Data collection

Patient demographics and clinical data were collected at the first day of meropenem treatment. Serial measurements of serum creatinine (daily), C-reactive protein (daily) and procalcitonin (less frequently) were performed before, during and after the initiation of meropenem therapy.

5.2.3. Meropenem administration and sample collection

Meropenem doses of 0.5, 1 or 2 g every 8 h were used for initial, empiric therapy. Doses were selected by the attending clinician. All patients received a loading dose of 1000 mg meropenem as short-term infusion. The second and all subsequent doses were given as 3-h infusions via a high precision infusion pump through a central venous catheter. The infusion line was rinsed with saline at the same rate as the meropenem infusion to assure complete dosing of meropenem. Actual durations of infusion were recorded and used for modeling.

Blood samples (2 mL) were drawn from an arterial line at the end of infusion (“peak”), as well as two hours before and immediately before (“trough concentration”)

the next infusion. Blood samples were collected in K_3-EDTA tubes and immediately cooled in an ice water bath for at least 5 min. Within 15 min, samples were centrifuged at +4 °C and the resulting plasma was immediately frozen and stored at -80 °C until analysis.

5.2.4. Quantification of meropenem concentrations

Meropenem concentrations were quantified using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay developed at the IBMP by Christoph Stelzer and Martina Kinzig. Analysis of independently prepared quality control samples indicated good reproducibility as the resulting coefficient of variation was in the range of 5.1 to 8.5 % and the accuracy of these quality control samples was in the range of 98.0 to 102.9 % (measured concentrations vs. target concentrations). The limit of quantification was 0.5 mg/L.

The liquid chromatography systems consisted of a binary LC-pump (Agilent 1200 Series, Agilent Technologies, Waldbronn, Germany) and an analytical column (Spherisorb Phenyl, 5 µm, 60 x 4.6 mm, Waters GmbH, Eschborn, Germany). Isocratic elution was performed with 0.005 M ammonium acetate buffer (75 %) and acetonitrile (25 %). Determination was performed using an AB SCIEX API 5000 triple quadrupole mass spectrometer (AB SCIEX, Concord, Ontario, Canada) and Analyst software version 1.6.2 (AB SCIEX, Concord, Ontario, Canada). In brief, 50 µL of each sample was placed in a polypropylene-tube. Samples were deproteinized with 150 µL acetonitrile (containing the internal standard levofloxacin), subsequently vortex-shaked and centrifuged. The supernatant was further diluted with 0.001 M ammonium acetate buffer and 30 µL of each samples were injected into the LC-MS/MS system. The samples for meropenem were detected with MRM (Multiple Reaction Monitoring) as follows: precursor → product ion for imipenem 384.00 → 114.10 m/z and for levofloxacin (internal standard) 362.00 → 261.10 m/z; for all analytes in positive mode. Under these conditions imipenem eluted after 1.0 minutes and the internal standard after 2.0 minutes.

5.2.5. Dose adjustment

Dose adjustment was recommended if the meropenem trough concentration was outside the targeted range of 2 to 16 mg/L. Dose adjustment was performed, but

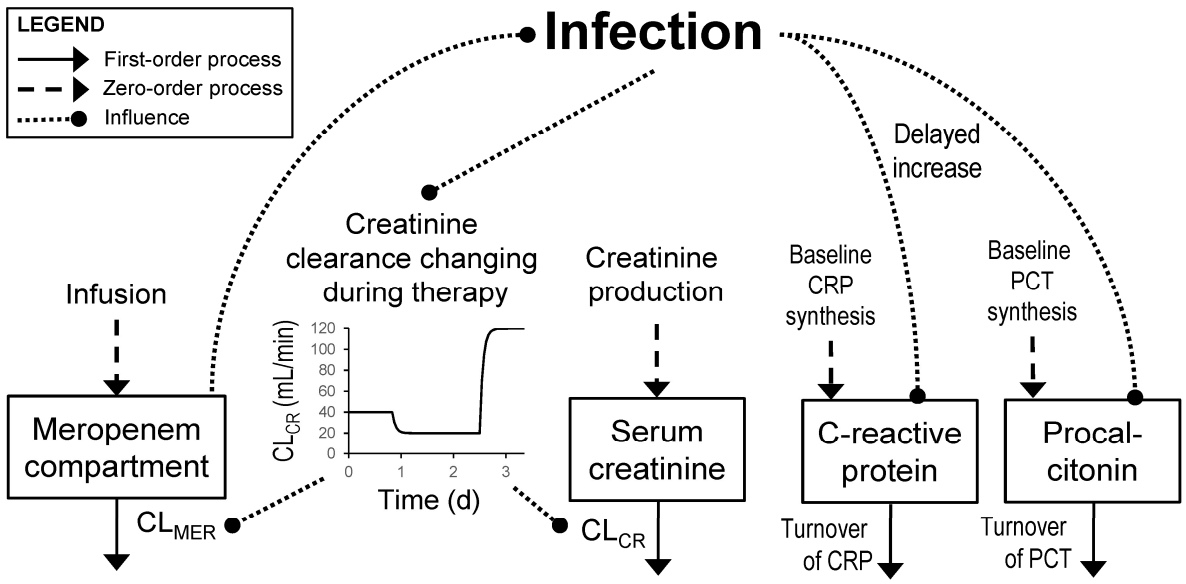
could not exceed the maximum approved dose of 2 g meropenem every 8 h. The smallest dose was 500 mg meropenem every 8 h to assure that patients are not under-dosed. The attending physician ultimately decided whether dose adjustment was clinically warranted and performed.

5.2.6. Population Pharmacokinetic Modeling

Structural model: We developed a new population pharmacokinetic / pharmacodynamic model that simultaneously described the time-course of meropenem, serum creatinine, C-reactive protein, and procalcitonin in all patients (Figure 5-1). Creatinine clearance was allowed to change twice over time at random time points in each patient. The time-course of creatinine clearance was informed by both the meropenem and serum creatinine concentrations. Meropenem and creatinine were each described by a linear one-compartment model. Creatinine is predominantly cleared by glomerular filtration[96,174] and meropenem is both filtered and subject to active tubular secretion via hOAT1 and hOAT3[176]. To evaluate meropenem dose adjustment based on creatinine clearance in ICU patients, we considered linear and nonlinear relationships to correlate meropenem clearance with creatinine clearance.

The concentrations of meropenem, serum creatinine and of the infection biomarkers C-reactive protein and procalcitonin were all simultaneously modeled (Figure 5-1, and supplementary materials in the appendix). Details on the modeling are provided in the supplementary materials[97–100,177].

Figure 5-1 Structural model for meropenem, serum creatinine, C-reactive protein (CRP) and procalcitonin (PCT).



Infection leads to increased CRP and PCT concentrations after a time-delay. Additionally, an infection can lead to substantial and rapid changes of creatinine clearance (i.e. renal function) over time. In the population PK model, creatinine clearance affected both the elimination of serum creatinine and meropenem in the model. The baseline synthesis of CRP and PCT were very small compared to the increases of CRP and PCT following an infection.

5.2.7. Non-compartmental analysis (NCA)

The non-compartmental analysis (NCA) was performed with the same methods and equations as the NCA of the imipenem / cilastatin data in chapter 3 of this thesis. Therefore, in a first step, the means of the trough and peak plasma levels, dosages and the duration of the dosing intervals were calculated for each patient. With this data, the average steady state concentration ($c_{ss\ av.}$), the area under the curve (AUC) and the clearance (CL) for each individual were calculated using equation 6, 9 and 10:

$$CL = \frac{Dose}{AUC}$$ *Equation 6*

$$AUC = c_{SS} * \tau$$ *Equation 9*

$$c_{av.}^{SS.} = \frac{c_{\max}^{SS} - c_{\min}^{SS}}{\ln\left(\frac{c_{\max}^{SS}}{c_{\min}^{SS}}\right)}$$ *Equation 10*

Finally, the resulting clearance was correlated with renal function, expressed by creatinine clearance (estimated by the Cockcroft and Gault formula) and was compared to the clearance obtained by the population pharmacokinetic approach.

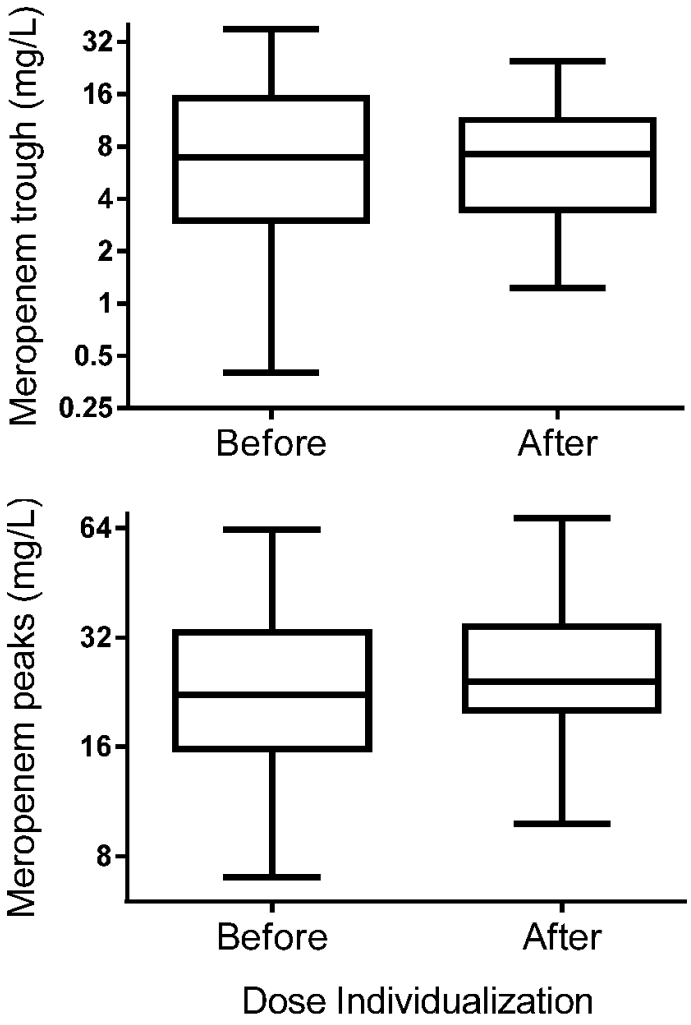
5.3. Results

This study included 53 ICU patients with a median baseline creatinine clearance of 67.9 (range: 6.41 to 250) mL/min according to the Cockcroft & Gault formula (Table 5-1). Patients received an average number of 16 meropenem doses [range 3 to 44]. In total, 469 plasma concentrations were available for modeling with a median [5^{th} to 95^{th} percentile] of 9 [3 to 16] samples per patient. Meropenem peak concentrations after a 3-h infusion were 25.8 ± 12.9 mg/L (average ± SD; following a dose of 1 g meropenem every 8 h in the vast majority of patients). Meropenem trough concentrations before dose adjustment were 9.90 ± 8.62 mg/L (range: <0.5 mg/L [below quantification limit] to 37.9 mg/L). One patient only had a meropenem peak concentration but no trough concentration. Without dose adjustment, 50% (26 of 52) of the patients had a trough concentration in the target range from 2 to 16 mg/L. Target concentrations were achieved much more precisely after dose adjustment compared to before dose adjustment (Figure 5-2).

Table 5-1 Population characteristics.

Parameter	Value [median (range) or No. (%)]	
No.	53	
Age (yr)	67	(40 - 94)
Total body weight (kg)	80	(51 - 160)
Height (cm)	172	(150 - 192)
Body mass index (kg/m²)	26.1	(18.5 - 66.6)
Sex		
Male	37	(69.8)
Female	16	(30.2)
Baseline serum creatinine (mg/dL)	1.08	(0.34 - 13.9)
Baseline creatinine clearance by Cockcroft & Gault (mL/min)	67.9	(6.41 - 250)
With renal replacement therapy		
Continuous renal replacement	7	(13.2)
Sepsis		
No	13	(24.5)
Yes	40	(75.5)
Septic shock	36	(67.9)

Figure 5-2 Measured meropenem trough and peak concentrations before and after dose individualization.



One trough concentration before dose adjustment was below the lower limit of quantification and was plotted at 0.4 mg/L.

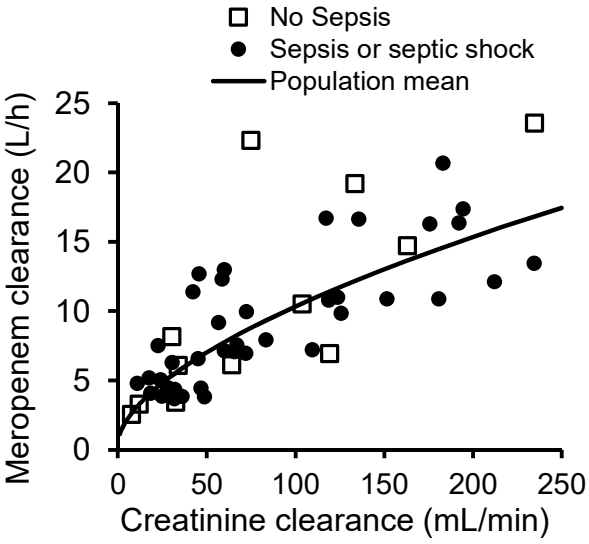
For 13 of the 26 patients with meropenem concentrations outside the targeted range, dose adjustment was considered clinically warranted, performed and subsequent meropenem trough concentrations monitored. Eleven of these 13 patients had trough concentrations within the target range after dose adjustment. One of the two patients outside the target range had a trough of 1.54 mg/L meropenem despite receiving the maximum dose (2 g every 8 h); the other patient received the lowest dose (0.5 g every 8 h) and had a trough concentration of 19.7 mg/L. For the latter patient, creatinine clearance changed substantially over time with an improvement by 52% being followed by a deterioration by 57%. As these two patients would have required

dose adjustment outside of 0.5 to 2 g meropenem every 8 h, they were excluded from the statistical analysis. Therefore, target trough concentrations were successfully achieved in 11 of 11 patients after dose adjustment. This was superior ($p<0.001$, Fisher's exact test) to the 50% frequency (26 of 52 patients) of achieving the targeted trough concentration range before dose adjustment.

5.3.1. Results of population PK analysis

Our population PK analysis identified a nonlinear relationship between meropenem clearance and creatinine clearance (Figure 5-3). The total meropenem clearance (in L/h for patients with 70 kg total body weight) was 0.480 L/h + 9.86 L/h · $(CL_{CR}/6\ L/h)^{0.593}$ (Table 13-1) with 0.480 L/h representing the nonrenal clearance and the second term the renal clearance. Renal meropenem clearance increased significantly less than linearly with creatinine clearance ($p<0.001$).

Figure 5-3 Nonlinear relationship of meropenem clearance vs. creatinine clearance for 53 patients receiving meropenem.

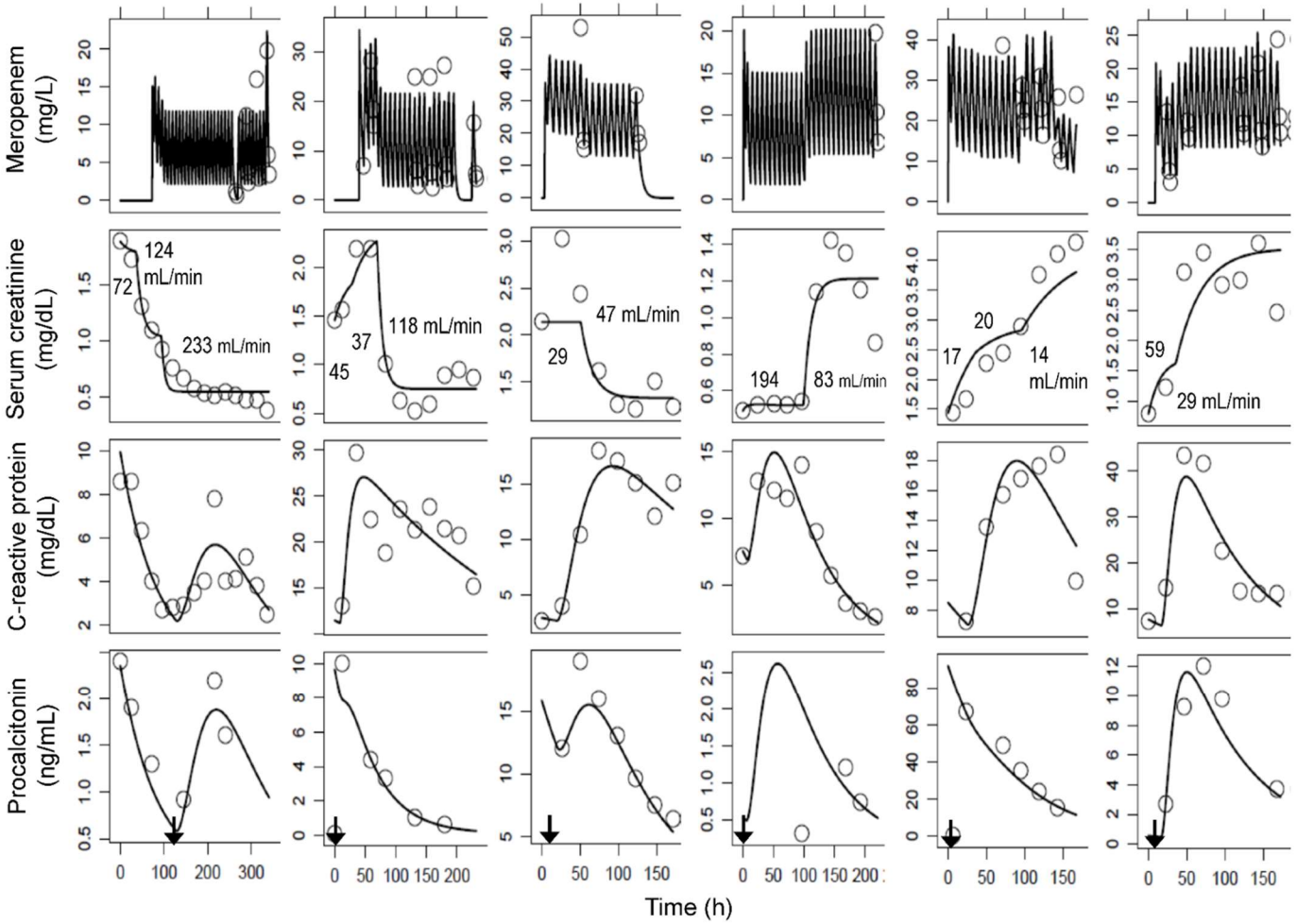


Our population model allowed creatinine clearance to change over time (Figure 5-1) which affected both the time-course of meropenem and creatinine concentrations. Renal function changed substantially and rapidly in ICU patients. The half-life of change in renal function was estimated to be 0.516 h (Table 13-1). Our model allowed for up to two changes in renal function over time (Figure 5-1). The first change occurred at 1.70 [0.692 to 2.37] days (median [range]) and the second change occurred at 4.79

[1.46 to 7.14] days post enrollment in the study. Enrollment was at 0.82 [0.00 to 40.1] h (median [10^{th} to 90^{th} percentile]) before the first meropenem dose. The final model provided adequate curve fits of serum creatinine and of meropenem concentrations as shown in Figure 5-4.

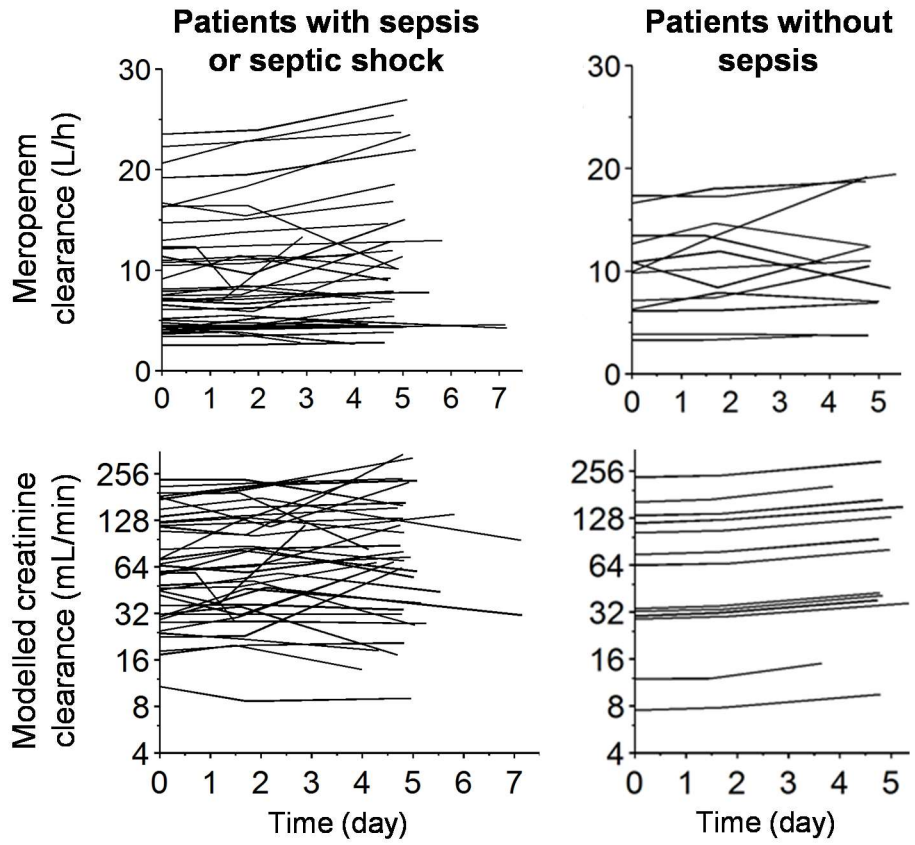
Similarly, the final model provided highly acceptable curve fits for the C-reactive protein and procalcitonin given the complex profiles of these infection markers (Figure 5-4). An infection caused an increase in the C-reactive protein and procalcitonin concentrations and could affect creatinine clearance in both directions. There was no obvious correlation between the increases or time points of increase of C-reactive protein or procalcitonin with the observed changes in renal function. The half-life of turnover was 93.1 h (66.1% CV representing between patient variability) for C-reactive protein, but much shorter (46.9 h) and less variable (28.0% CV) for procalcitonin (Table 13-1).

Figure 5-4 Observed (markers) and individually fitted (lines) concentrations of meropenem in plasma (row 1), serum creatinine (row 2), C-reactive protein (row 3), and procalcitonin (row 4).



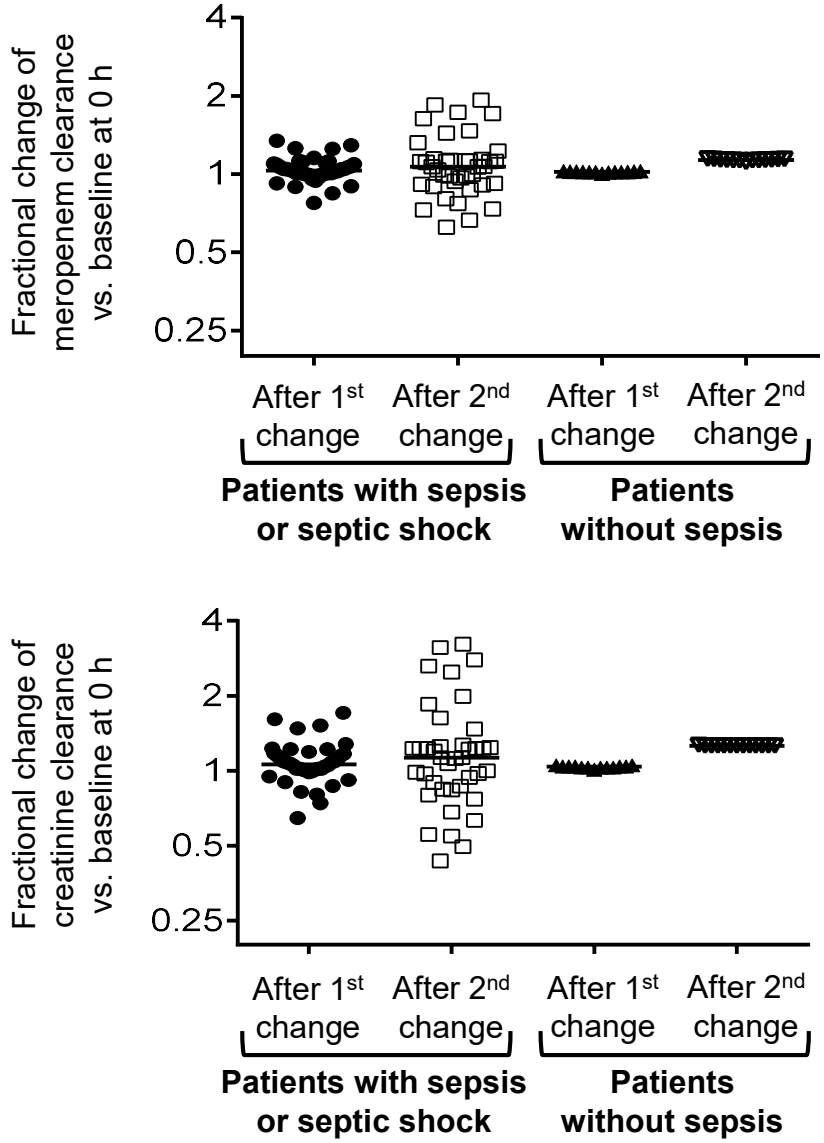
Each column represents one patient. In the 2nd row, the estimated changes in creatinine clearance over time are reported. Arrows on the time-axis indicate the estimated times of infection.

Figure 5-5 Change in creatinine clearance and meropenem clearance over time in patients with sepsis (n=4) and septic shock (n=36; left side) compared to patients without sepsis (n=13; right side).



Creatinine clearance was allowed to change twice over time. The first change occurred on average after 28.0 h and the second change after approximately 5 days. Between patient variability in the changes in renal function were substantially more pronounced in patients with sepsis or septic shock compared to patients without sepsis.

Figure 5-6 Fractional changes in clearance over time for meropenem (top panel) and creatinine (bottom).



The left two columns refer to patients with sepsis or septic shock and the right two columns to patients without sepsis. The markers are the individual estimates in each patient and the bar represents the median.

5.3.2. Results of the non-compartmental analysis

Four patients were excluded from the analysis due to missing trough or peak plasma levels.

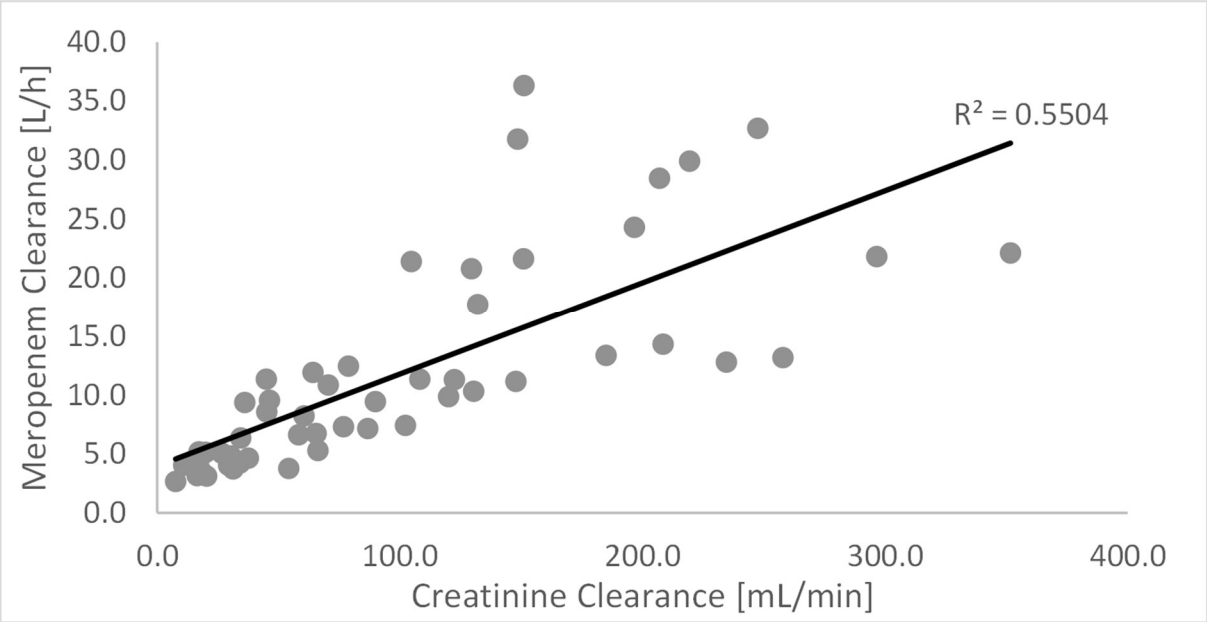
The resulting mean ± SD peak and trough plasma levels of meropenem of all remaining patients were 26.6 ± 11.4 µg/mL and 9.9 ± 7.9 µg/mL. This data resulted in

an average steady state concentration of meropenem of 16.5 ± 9.5 µg/mL. The average duration of an infusion interval was 7.9 ± 0.5 h.

The resulting mean ± SD area under the curve and clearance of meropenem was 130.8 ± 75.3 µg*h/mL and 11.9 ± 8.7 L/h.

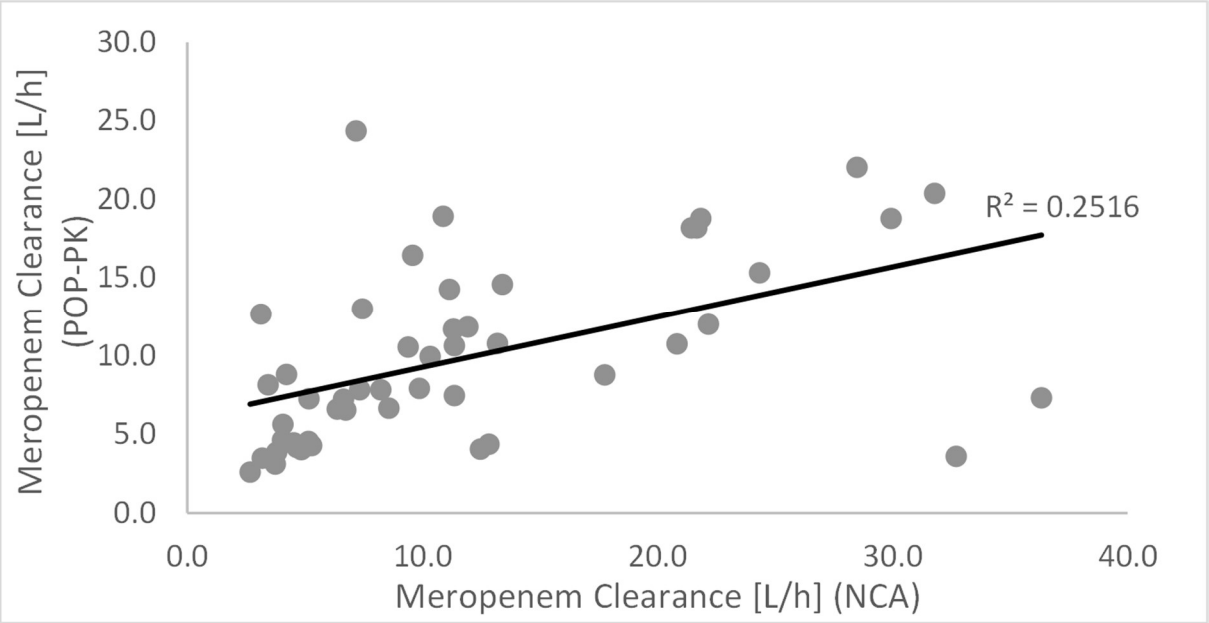
Meropenem clearance was in good correlation with creatinine clearance, showing a correlation coefficient (r) of 0.742 ($p<0.001$). A graphical representation of this correlation is shown in Figure 5-7.

Figure 5-7 Correlation plot of meropenem clearance vs. creatinine clearance.



Meropenem clearance obtained by non-compartmental analysis (NCA) correlated with the clearance obtained by the population pharmacokinetic (POP-PK) approach, resulting in a correlation coefficient (r) of 0.502 ($p<0.001$). However, some results differ significantly between the two methods as can be seen in Figure 5-8.

Figure 5-8 Correlation plot of meropenem clearance (POP-PK) vs. meropenem clearance (NCA)



5.4. Discussion

This study presents the first population PK analysis for meropenem in a large population of ICU patients and identified a nonlinear relationship between creatinine clearance and meropenem clearance. The proposed new modeling approach uses meropenem and creatinine concentrations to characterize the changes of renal function over time. This enabled us to model the rapid changes of renal function. This approach is fully amenable to handle unstable patients with rapid and extensive changes of renal function over time such as ICU patients with sepsis or septic shock.

Our analysis demonstrated that renal function could change rapidly (within <1 h) and extensively in patients with sepsis and septic shock (Figure 5-5 and Figure 5-6). It took significantly longer for creatinine concentrations to achieve the new steady-state (Figure 5-4). This suggests that creatinine may not be at steady-state in ICU patients with sepsis or septic shock. Dosing of ICU patients with unstable PK is currently usually done empirically and TDM is not common to individualize meropenem dosing[114].

We propose to directly measure meropenem concentrations in a clinically feasible TDM algorithm, as performed here, to individualize meropenem dosing. As the terminal half-life of meropenem is short, meropenem concentrations adapt much more quickly to the extensive changes in renal function of ICU patients compared to the

changes in serum creatinine concentrations. Therefore, clinically relevant changes in renal function can be efficiently identified and accounted for by TDM of meropenem.

Without TDM, 50% of the ICU patients in our study had meropenem concentrations outside the target range (Figure 5-2). We could show that TDM significantly improved the likelihood of achieving the target concentration range. Before the result of the first TDM sample becomes available, high meropenem doses (e.g. 1 or even 2 g) at 0, 8, and 16 h are recommended. This maximizes the likelihood for achieving effective meropenem concentrations on day 1. The available TDM data on meropenem plasma concentrations during the first day of therapy supported dose selection starting on day 2 and later.

Our population PK analysis identified a significantly nonlinear relationship between meropenem clearance and creatinine clearance (Figure 5-3). Meropenem clearance increased considerably less than linearly with creatinine clearance. This may be particularly important for patients with creatinine clearance between 20 and 50 mL/min, since those patients required 35 to 96% higher meropenem doses than predicted by a linear relationship.

The proposed model is fully amenable to handle patients with unstable and rapidly changing renal function. This implementation of the model included two changes of renal function over time which was sufficient to provide reasonable curve fits for meropenem and serum creatinine concentrations (Figure 5-4). We chose a one-compartment model to describe the meropenem concentrations after a prolonged infusion whereas some previous studies used multi-compartment models to describe meropenem when given as a short-term infusion[109,116,120,138]. Our long infusion duration and relatively sparse sampling likely contributed to the observation that a one-compartment model was suitable for our dataset.

Our estimates of 9.86 L/h for renal clearance in patients with 6.0 L/h creatinine clearance and of 0.480 L/h for nonrenal clearance fell within the range of previous clearance estimates in patients (Figure 4-7). Likewise, our estimated volume of distribution at steady-state was well comparable to the estimates from other studies (Figure 4-8). Therefore, the PK parameter estimates from our study were in agreement with previously reported estimates for meropenem.

In addition to modeling meropenem and serum creatinine, we included procalcitonin and C-reactive protein in our population model to characterize the time-course of these infection biomarkers. The between patient variability in these biomarker profiles was high. The estimated half-life of procalcitonin (47.1 h) was considerably shorter than that of C-reactive protein (96.8 h). Moreover, the variability of the half-life of procalcitonin was substantially smaller (28.0% coefficient of variation) than the variability of half-life for C-reactive protein (66.1%). The much shorter and less variable half-life of procalcitonin suggested that a decline in procalcitonin occurs more quickly and is more reliable to predict a lack of an ongoing infection.

In summary, renal clearance of meropenem and creatinine changed extensively and rapidly over time in patients with sepsis or septic shock. The proposed new population PK model excellently characterized these changes in renal function. Meropenem TDM provided a feasible and valuable approach to significantly enhance the probability of achieving meropenem concentrations in the targeted concentration range. We found a nonlinear relationship between meropenem clearance and creatinine clearance which may affect dosing of patients with creatinine clearances below 50 mL/min. Procalcitonin was estimated to be a potentially more useful biomarker for infection than C-reactive protein, since the elimination half-life of procalcitonin was about 2-fold faster and substantially less variable than that of C-reactive protein. Future clinical studies are warranted to explore the improvement of clinical outcomes for ICU patients with compared to without TDM of meropenem.

The results of the non-compartmental PK analysis of meropenem plasma levels demonstrate that this straightforward method can provide reliable PK results for most patients, even with scarce data.

However, several limitations of this approach should be considered. Firstly, the calculation of the average steady state concentration using equation 10 is only applicable in steady state conditions and a minimum of one peak and one trough plasma level per individual is necessary. Moreover, the peak and trough blood samples have to be collected as quickly as possible after the end of the infusion and directly before the start of the next infusion to provide reliable average steady state plasma concentrations. However, if drugs with short half-life as meropenem are administered

as prolonged infusions, steady state may be reached after few infusions and peak concentrations do not fluctuate as much as after short infusions.

Secondly, the NCA approach does not provide results for half-life and volume of distribution, as the elimination rate constant (ke) cannot be determined reliably with only one peak and one trough plasma level.

Finally, while most results of the NCA approach were in good correlation with the results of the POP-PK approach, some results differ significantly between both methods. The resulting clearances of two patients were estimated to be more than four times higher by the NCA approach than by the POP-PK approach (36.3 vs. 7.3 L/h and 32.7 vs. 3.6 L/h). On the opposite, the resulting clearances of two patients were estimated to be more than three times lower by the NCA approach than by the POP-PK approach (3.1 vs. 12.7 L/h and 7.2 vs. 24.4 L/h). Without these four patients, the correlation coefficient would rise from 0.502 to 0.806.

A possible explanation for the differing results between both approaches is that the renal clearance of meropenem and creatinine change extensively and rapidly over time in patients with sepsis. While these changes are incorporated in the population model, the NCA approach uses the means of all available blood levels of meropenem and creatinine of one patient.

6. Pharmacokinetics and bone penetration of ampicillin and sulbactam in patients undergoing total hip replacement surgery

6.1. Introduction

Surgical site infections (SSI) after total hip replacement surgeries are a severe complication which is associated with higher mortality, substantially higher costs, reduced quality of life and functional outcomes in affected patients[178,179]. Prophylactic antibiotic administration for hip surgery is in widespread clinical use and has been confirmed to reduce the incidence of postoperative wound infection[180–182].

The aim of antibiotic prophylaxis is to achieve plasma and tissue drug levels that exceed, for the duration of the operation, the minimum inhibitory concentrations (MIC) for the bacteria likely to be encountered during the operation[183]. Therefore, the two most important considerations when choosing an antibiotic for the prophylaxis of postoperative bone infections are its activity against bacteria likely to cause these infections, and the capacity of the antibiotic to penetrate tissues and in particular bone to reach concentrations above the MIC for the duration of the incision.

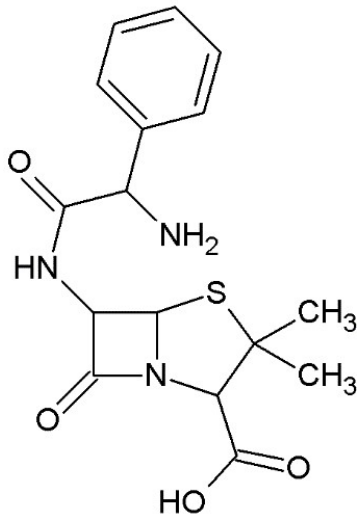
Ampicillin (Figure 6-1) is an extended spectrum penicillin of the aminopenicillin class, which has greater activity against gram-negative bacteria due to its enhanced ability to penetrate the outer membrane of gram-negative bacteria. Susceptible organisms to ampicillin include anaerobes, enterococci, *Listeria monocytogenes*, and beta-lactamase-negative strains of gram-negative strains of cocci and bacilli such as *Escherichia coli*, *Haemophilus influenzae* and Salmonella spp[184]. The co-administration of sulbactam (Figure 6-2) extends the antibiotic spectrum of ampicillin to beta-lactamase-producing strains of staphylococci, *Escherichia coli*, other gram-negative species, as well as anaerobes which are resistant to this penicillin alone[185]. Additionally, unlike other β-lactamase inhibitors, sulbactam possesses some direct antimicrobial activity, which includes Acinetobacter, Bacteroides and Neisseria species[186,187]. Belonging to the class of beta-lactam antibiotics, bacterial killing of ampicillin is largely dependent on the time the concentration of the unbound drug is above the MIC (fT>MIC). In vivo and in vitro studies have shown that the penicillin group of antibiotics requires 50–60% fT>MIC for maximum bactericidal activity[141,188].

According to the current “Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery”, the fixed combination of 2000 mg ampicillin and 1000 mg

sulbactam (Unacid®, Pfizer) is recommended as perioperative prophylaxis for different types of procedures[189]. However, for the prophylaxis of SSI in total hip replacement surgery, cefazolin or, alternatively clindamycin and vancomycin, are the only listed substances. Since the antimicrobial spectrum of ampicillin co-administered with sulbactam is at least equivalent to that of cefazolin, the combination of an aminopenicillin as ampicillin co-administered with a beta-lactamase inhibitor as sulbactam might be an adequate alternative in this setting.

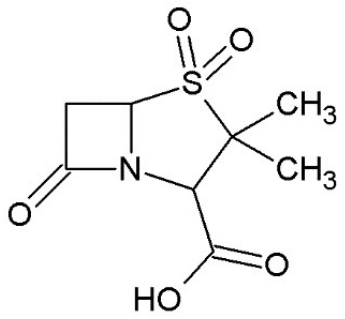
However, pharmacokinetic data of this combination in bone tissue and particularly in the setting of hip surgeries is sparse. In addition, none of the previous studies on bone pharmacokinetics of ampicillin and sulbactam provided information about the penetration of these drugs into the different bone types cortical and cancellous bone. Therefore, the aim of the present study was to investigate the pharmacokinetics of ampicillin and sulbactam in plasma and bone tissue in patients undergoing total hip replacement surgery with perioperative prophylaxis.

Figure 6-1 Structural formula of ampicillin.



($C_{16}H_{19}N_3O_4S$, Mol. Wt.: 349.4 g/mol)

Figure 6-2 Structural formula of sulbactam.



($C_8H_{11}NO_5S$, Mol. Wt.: 233.2 g/mol)

6.2. Methods

6.2.1. Study design and ethics

This study was an open-label, single-dose non-comparative investigation of the pharmacokinetics of ampicillin and sulbactam in plasma and of the degree of penetration of ampicillin and sulbactam into bone in patients undergoing total hip replacement surgery. The study was approved by the Institutional Review Board of the School of Medicine, Friedrich-Alexander-University Erlangen-Nürnberg, and was performed according to the revised version of the Declaration of Helsinki. The study is registered at the European Clinical Trials Database (EudraCT-number: 2012-002919-25).

6.2.2. Patients

Male or female patients with coxarthrosis who were scheduled to undergo total hip replacement surgery were eligible to participate in this study. Further inclusion criteria were 18-85 years of age, body mass index between 18 and 35 kg/m^2, supine heart rate between 50 and 100 beats per minute, agree to use an effective method of contraception and, if female, no currently present pregnancy. Patients must have signed the informed consent form and have the mental capability to understand it. Patients were excluded if they were breastfeeding, had a history of any hypersensitivity to beta-lactam antibiotics, inflammatory joint disease, cystic fibrosis, suspected rhabdomyolysis or anemia, defined as laboratory values of creatine kinase over 10,000 U/L, hemoglobin below 10 g/dL or hematocrit below 30%. Patients were also excluded if they received cotrimoxazole or cimetidine therapy initiated within about one day before surgery. Further exclusion criteria were supine systolic blood pressure below 90 or above 160 mm Hg, or supine diastolic blood pressure below 50 or above 95 mm Hg at screening, impaired renal function expressed as creatinine clearance below 50 mL/min (Cockcroft-Gault estimate), positive drug screen at screening (urine) and positive results for HIV, hepatitis B or hepatitis C virus at screening.

6.2.3. Study drug administration

A single dose of 2000 mg ampicillin in combination with 1000 mg sulbactam (Unacid®; PFIZER PHARMA GmbH, Berlin, Germany) was administered as a short-

term intravenous infusion to each patient at the induction of anesthesia. In addition, each patient received a single 60 min intravenous infusion of ceftaroline fosamil 1 to 8 h before bone resection.

6.2.4. Sample collection

Depending on the time of the infusion of ampicillin and sulbactam relative to the infusion of ceftaroline fosamil, patients received different numbers of blood samples. Dependent of the number of blood samples, patients were divided into five groups. Patients of group 1 received the infusion of ampicillin and sulbactam about 30 minutes before the infusion of ceftaroline fosamil. Blood samples of this group were taken about 0.3, 1.0, 1.4, 1.5, 1.7, 2.0, 2.5, 3.5, 4.5, 6.5, 8.5 and 12.5 h past start of the ampicillin and sulbactam infusion. Patients of group 2 received the infusion of ampicillin and sulbactam about 1.5 h past the infusion of ceftaroline fosamil. Samples of this group were taken before and about 0.1, 0.3, 0.6, 1.5, 2.5, 4.5, 6.5 and 10.5 h past start of the ampicillin and sulbactam infusion. Patients of group 3 received the infusion of ampicillin and sulbactam about 3.25 h past the infusion of ceftaroline fosamil. Samples of this group were taken before and about 0.6, 2.7, 4.7 and 8.7 h past start of the ampicillin and sulbactam infusion. Patients of group 4 received the infusion of ampicillin and sulbactam about 5.25 h past the infusion of ceftaroline fosamil. Samples of this group were taken before and about 0.6, 2.6 and 6.6 h past start of the ampicillin and sulbactam infusion. Patients of group 5 received the infusion of ampicillin and sulbactam about 7.5 h past the infusion of ceftaroline fosamil. Samples of this group were taken before and about 0.6 and 4.6 h past start of the ampicillin and sulbactam infusion. In all patients, one blood sample was taken at the time of bone resection.

Blood samples were collected by the responsible physician via either an central or peripheral indwelling venous catheter in a 4-mL gray-top Vacutainer® tube (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), containing 10 mg of sodium fluoride and 8 mg of potassium oxalate as anticoagulants. Before the sample was taken, 2 to 5 mL of blood were withdrawn to clear the line. After blood sample was drawn, the line was flushed with saline and the Vacutainer® tube was inverted gently 8-10 times to mix the blood with the anticoagulant. The blood samples were placed in an ice-water bath for 5 minutes before they were centrifuged at approximately 1500 g for 10 minutes in a refrigerated centrifuge (Beckman Coulter Allegra 6R; Beckman

Coulter, Inc., Brea, CA, USA) at 4°C. After centrifugation, the plasma samples were immediately transferred into two to three 2 mL pre-labeled polypropylene tubes using a disposable pipette. Thereafter, the aliquoted samples were immediately frozen in liquid nitrogen and stored at -80 °C until the analysis.

The hip replacement surgery consisted of resection of the femoral head and the subsequent implantation of the prosthetic hip joint. The bone sample was collected by the surgeon operating on the patient and the responsible physician then cut the bone material of the femoral head into pieces (Figure 6-3 to 6-5), removed adhering connective tissue and separated cancellous (Figure 6-6) from cortical bone (Figure 6-7). The adhering blood was removed from the samples by swabbing for a short time using a slightly wet (saline) cotton tissue. The collected cortical and cancellous bone specimens were placed in 5 mL pre-labeled polypropylene tubes and immediately frozen with liquid nitrogen and stored at -80°C until analysis.

Figure 6-3 Dissection of femoral head (1).

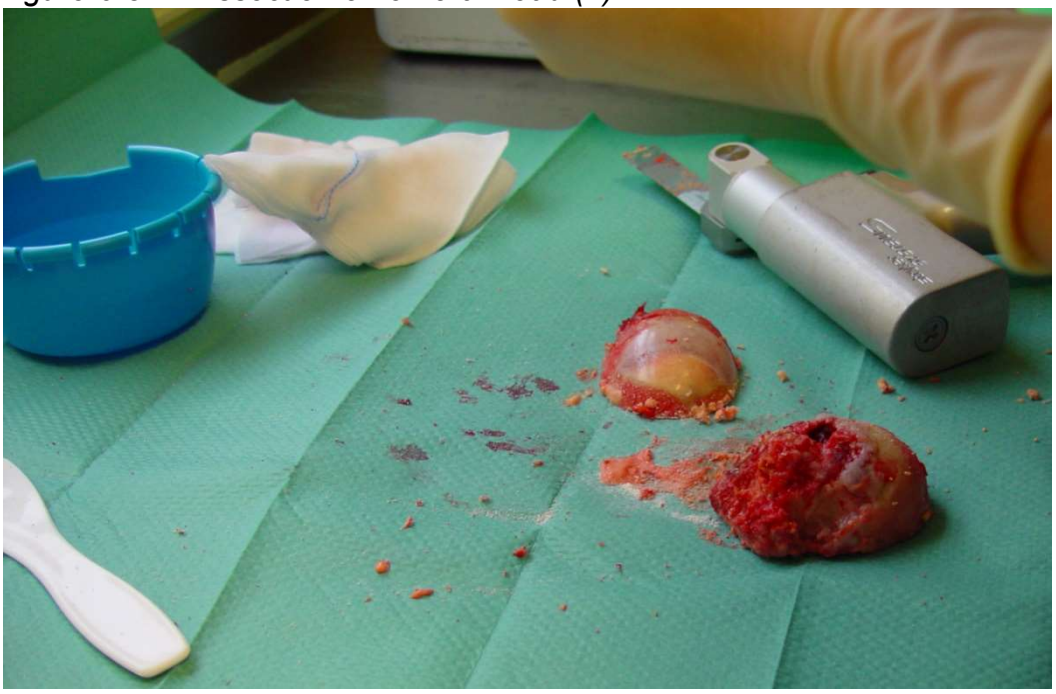


Figure 6-4 Dissection of femoral head (2).

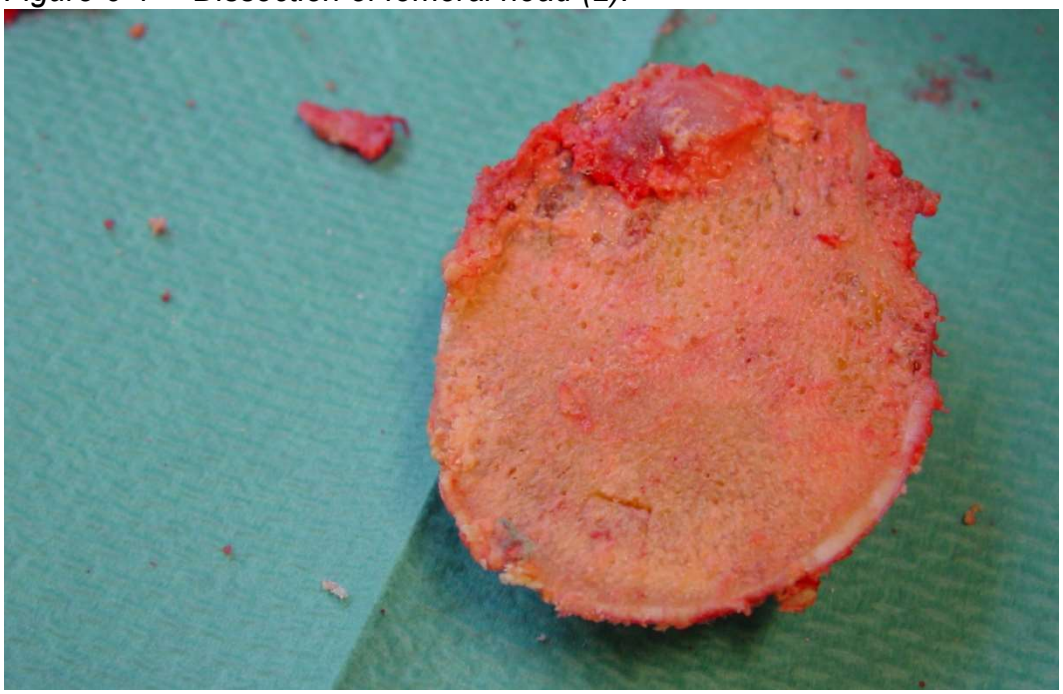
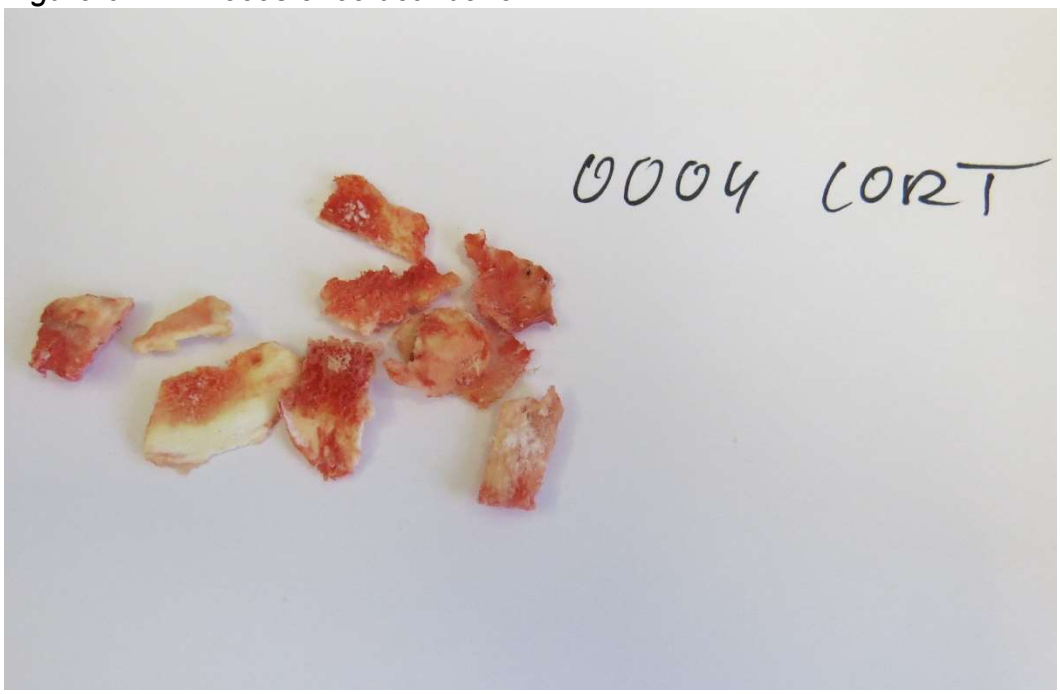


Figure 6-5 Dissection of femoral head (3).

Figure 6-6 Pieces of cancellous bone.

Figure 6-7 Pieces of cortical bone.



6.2.5. Determination of plasma and bone concentrations

Christoph Stelzer and Martina Kinzig developed the analytical methods for the determination of ampicillin and sulbactam in human plasma and bone at the IBMP.

In brief, acetonitrile was used for deproteinizing the plasma samples. After centrifugation, the supernatant was analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Bone samples were pulverized under liquid nitrogen by use of a cryogenic mill (6850 Freezer Mill, Spex CertiPrep, Metuchen, NJ, USA). The pulverized bone sample was extracted with buffer; after centrifugation, the supernatant was analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Ampicillin-d5 was used as internal standard for ampicillin and tazobactam was used as internal standard for sulbactam. The lower limit of quantification (= lowest calibration point) in plasma was 0.10 µg/mL for ampicillin and 0.05 µg/mL for sulbactam. The lower limit of quantification (= lowest calibration point) in bone was 21.4 ng/mL (in homogenate) for ampicillin and 21.3 ng/mL (in homogenate) for sulbactam.

The liquid chromatography systems consisted of a binary LC-pump (Agilent 1200 Series, Agilent Technologies, Waldbronn, Germany) and an analytical column (Kinetex 2.6 u C18, 100 A, 50 x 4.6 mm, Phenomenex, Aschaffenburg, Germany). Gradient elution was performed with 0.1 % formic acid and acetonitrile. Determination

was performed using an AB SCIEX API 5000 triple quadrupole mass spectrometer (AB SCIEX, Concord, Ontario, Canada) and Analyst software version 1.6.2 (AB SCIEX, Concord, Ontario, Canada). In brief, 50 µL of each human plasma sample was placed in a polypropylene-tube. Samples were deproteinized with 300 µL acetonitrile (containing the internal standards ampicillin-d5 and tazobactam), subsequently vortex-shaked and centrifuged. The supernatant was further diluted with 0.1 % formic acid and 10 µL of (ampicillin) or 50 µL (sulbactam) of each samples were injected into the LC-MS/MS system.

All human cancellous and cortical bone samples of the subjects were pulverized in liquid nitrogen using a Freezer/Mill 6850 (Program used: 2 Cycles with 3 minutes and rate 10). The bone powder samples were stored at -70 °C until analysis. 50 mg of each human pulverized bone sample was placed in a polypropylene-tube and 300 µL buffer (65 % Milli-Q®-water, 10 % sodium dihydrogen phosphate buffer, 5 % methanol, 20 % acetonitrile) was added. The samples were extracted for 20 minutes and centrifuged. 50 µL of the supernatant were deproteinized by 250 µL acetonitrile containing the internal standards (ampicillin-d5 and tazobactam), subsequently vortex-shaked and centrifuged. The supernatant was further diluted with 0.1 % formic acid and 10 µL of (ampicillin) or 50 µL (sulbactam) of each samples were injected into the LC-MS/MS system. The plasma and bone samples for ampicillin and sulbactam were detected with MRM (Multiple Reaction Monitoring) as follows: precursor → product ion for ampicillin 350.00 → 160.00 m/z, for ampicillin-d5 (internal standard for ampicillin) 355.00 → 111.40 m/z; for sulbactam 232.20 → 140.10 m/z and for tazobactam (internal standard for sulbactam) 299.20 → 137.90 for ampicillin and ampicillin-d5 in positive mode and for sulbactam and tazobactam in negative mode. Under these conditions ampicillin and ampicillion-d5 eluted after 2.4 minutes, sulbactam eluted after 1.3 minutes and tazobactam (internal standard for sulbactam) after 1.1 minutes.

6.2.6. Pharmacokinetic analysis

Pharmacokinetic parameters of ampicillin and sulbactam were determined using non-compartmental analysis. First, the elimination rate constant ke was determined from log-linear least squares regression analysis of concentrations from 2 h to the last sample collected before the next dose. With ke, the terminal half-life ($t_{1/2}$) was calculated using the equation:

$$t_{1/2} = \frac{\ln(2)}{ke}$$ *Equation 5*

The next pharmacokinetic parameter that was determined was the total area under the concentration-time curve (AUC $_{0-\infty}$). The $AUC_{0-\infty}$ is composed of the area under the concentration-time curve from zero to the time of the last sample collected (AUC_{0-t}) and the area under the concentration-time curve from the last sample collected to infinity ($AUC_{t-\infty}$) as shown by the equation:

$$AUC_{0-\infty} = AUC_{0-t} + AUC_{t-\infty}$$ *Equation 10*

For the calculation of the AUC_{0-t} the linear trapezoidal rule was used. The $AUC_{t-\infty}$ was calculated using the equation:

$$AUC_{t-\infty} = \frac{c_t}{ke}$$ *Equation 11*

The total body clearance (CL_T) and the volume of distribution (Vd) were calculated using the equations:

$$CL_T = \frac{Dose}{AUC_{0-\infty}}$$ *Equation 12*

$$Vd = \frac{CL_T}{ke}$$ *Equation 13*

6.2.7. Bone Penetration

Bone penetration (BP) was calculated as the ratio of the concentrations of ampicillin and sulbactam in cortical and cancellous bone and the concentrations of ampicillin and sulbactam in plasma as shown in the equation:

$$BP = \frac{c(bone)}{c(plasma)}$$ *Equation 14*

Cortical and cancellous bone concentrations and plasma concentrations of ampicillin and sulbactam as well as the bone penetration ratio were plotted against time in order to show the temporal course of the penetration of these substances from plasma into these bone tissues.

6.2.8. Statistical analysis

The Pearson correlation coefficient (r) was used as a measure of the degree of linear dependence between two variables (e.g. half-life and creatinine clearance). The

calculations for the determination of “r” and the corresponding “p-value” were carried out using standard Excel cell formulas.

6.3. Results

6.3.1. Demographical data of study patients

Twenty patients (13 female, 7 male) completed the study. Their detailed patient characteristics are listed in Table 6-1. With the exception of one patient who was suffering from hip dysplasia (age: 34 years), all patients were of mid to higher age (53 to 84 years). The average patient was slightly overweight with a mean BMI of 29.8 kg/m^2 (range 19.48 to 37.83) and had normal to slightly impaired renal function with a mean creatinine clearance (estimated by the Cockcroft and Gault formula) of 101.7 mL/min (range 52.3 to 176.3). One patient was included though not meeting the inclusion criteria due to his BMI of 37.8 kg/m^2.

Table 6-1 Demographical data of study patients.

		age [yr]	sex [m/f]	height [cm]	weight [kg]	BMI [kg/m^2]	serum creatinine [mg/dL]	creatinine clearance [mL/min]
Group 1	Patient 5	34	f	160	68	26.6	0.53	160.6
Group 1	Patient 9	72	m	169	88	30.8	1.04	79.9
Group 1	Patient 14	64	f	155	56	23.3	0.81	62.0
Group 1	Patient 16	72	f	178	80	25.3	0.77	83.4
Group 2	Patient 1	73	f	168	78	27.6	0.74	83.4
Group 2	Patient 7	70	f	152	80	34.6	0.65	101.7
Group 2	Patient 13	79	f	167	97	34.8	0.86	81.2
Group 2	Patient 20	59	m	172	102	34.5	0.77	149.0
Group 3	Patient 3	82	m	170	101	35.0	1.29	63.1
Group 3	Patient 6	78	f	152	45	19.5	0.63	52.3
Group 3	Patient 12	51	f	169	80	28.0	0.77	109.2
Group 3	Patient 19	82	f	165	78	28.7	0.62	86.1
Group 4	Patient 4	67	m	163	78	29.4	1.02	77.5
Group 4	Patient 8	64	m	172	93	31.4	0.63	155.8
Group 4	Patient 15	53	f	165	103	37.8	0.6	176.3
Group 4	Patient 17	64	f	174	100	33.0	0.84	106.8
Group 5	Patient 2	71	m	181	79	24.1	0.66	114.7
Group 5	Patient 10	84	f	164	70	26.0	0.54	85.7
Group 5	Patient 11	68	m	173	98	32.6	0.72	135.6
Group 5	Patient 18	79	f	157	79	32.1	0.81	70.2
Mean		**68.3**		**166.3**	**82.7**	**29.8**	**0.77**	**101.7**
SD		**12.3**		**8.1**	**15.6**	**4.7**	**0.19**	**36.1**

6.3.2. Number of blood samples within group 1 to 5 and plasma concentrations of ampicillin and sulbactam over time

According to the study protocol, patients received varying numbers of blood samples for the determination of ampicillin and sulbactam plasma levels depending on the group they were assigned. Plasma concentration vs time plots of ampicillin (a) and sulbactam (b) for each group are shown in Figure 6-8 to 6-17.

Twelve blood samples were collected from patients of group 1 for the determination of ampicillin and sulbactam concentrations in plasma. The last sample

of patient 5 was below the quantification limit of 0.1 µg/mL. Patient 16 received accidentally a second dose of 2000 mg ampicillin and 1000 mg sulbactam 33 minutes after start of the first infusion, which explains the occurrence of a “second” peak level of 273.5 µg/mL at 0.98 h past start of infusion. Therefore, this sample was not considered as peak level and the resulting pharmacokinetic parameters in plasma and bone of this patient were excluded from the calculation of the means of the study population. Patient 14 received a second dose of ampicillin/sulbactam before the last sample was drawn and therefore the last plasma concentration of this patient was not considered in the pharmacokinetic analysis.

Seven (patient 1 and 20) or eight blood samples (patient 7 and 13) were collected from patients of group 2. The first sample of each patient was drawn before start of ampicillin and sulbactam infusion and as a result was below the quantification limit. The second sample of patient 1 was taken only 0.05 h after start of the infusion and was below the quantification limit. Therefore, the third sample was considered as peak level. The first blood sampling in patient 20 was during the infusion (7 min past start and 7 min before end of infusion) and this patient received a second dose of ampicillin/sulbactam before the last sample was drawn. Therefore, the last plasma concentration of this patient was not considered in the calculation of the individual pharmacokinetic parameters of this patient and the resulting pharmacokinetic parameters in plasma and bone were excluded from the calculation of the means of the study population.

Five (patient 3, 6 and 19) or four (patient 12) blood samples were taken from patients of group 3. The first sample of each patient was drawn before start of ampicillin and sulbactam infusion and as a result, was below the quantification limit.

Four blood samples were collected of patients of group 4 and three blood samples were collected from patients of group 5. In both groups, the first sample of each patient was drawn before start of ampicillin and sulbactam infusion and as a result was below the quantification limit. Therefore, the pharmacokinetic parameters of patients of group 5 could not be determined.

Figure 6-8 Ampicillin plasma concentration vs time in patients of group 1.

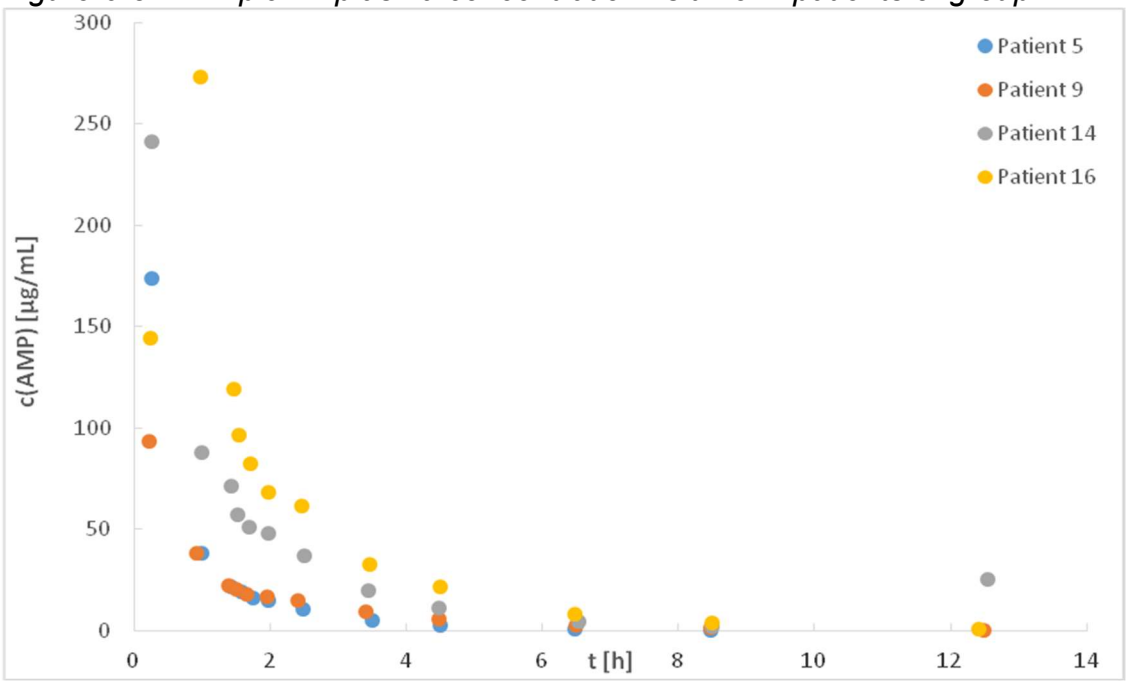


Figure 6-9 Sulbactam plasma concentration vs time in patients of group 1.

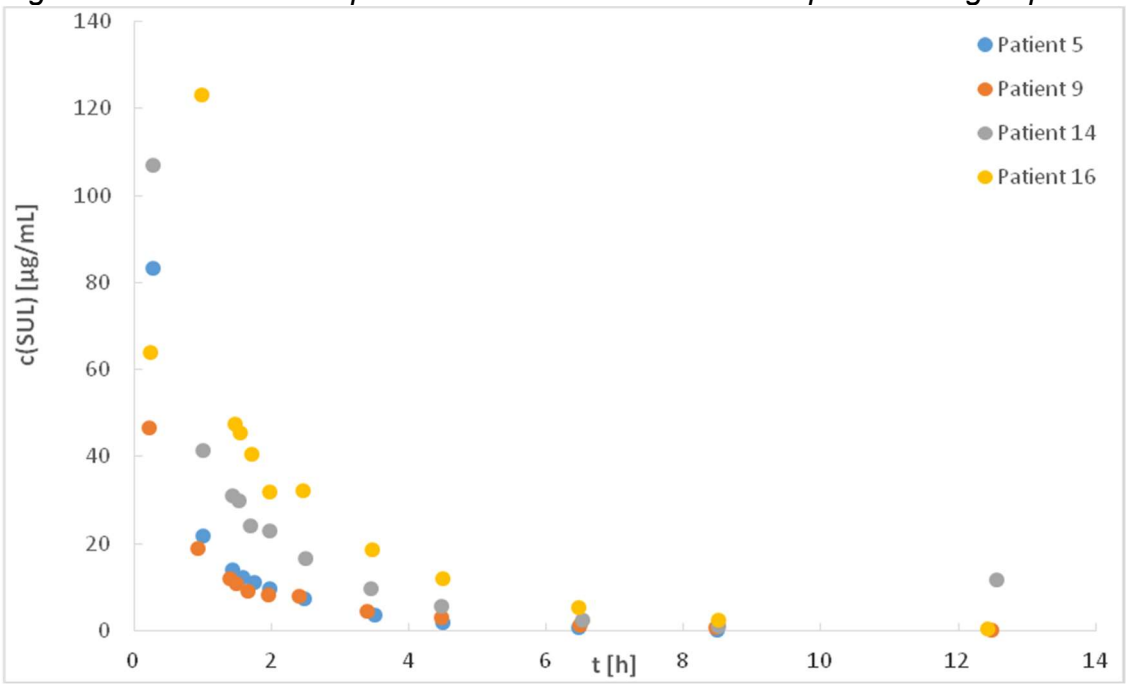


Figure 6-10 Ampicillin plasma concentration vs time in patients of group 2.

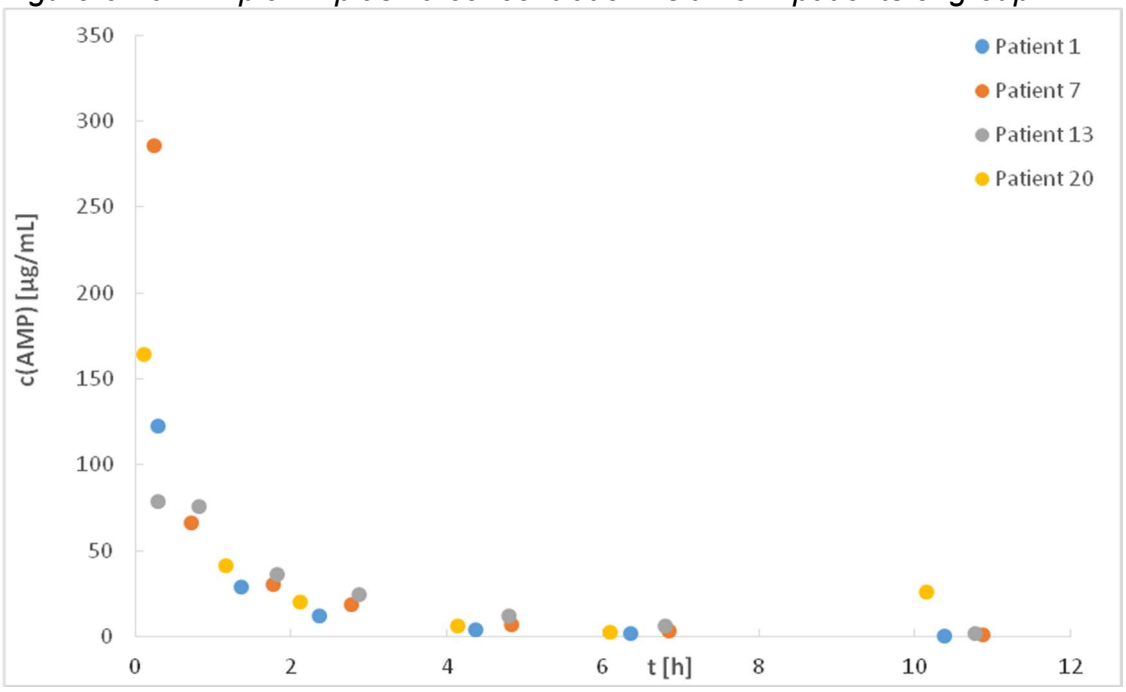


Figure 6-11 Sulbactam plasma concentration vs time in patients of group 2.

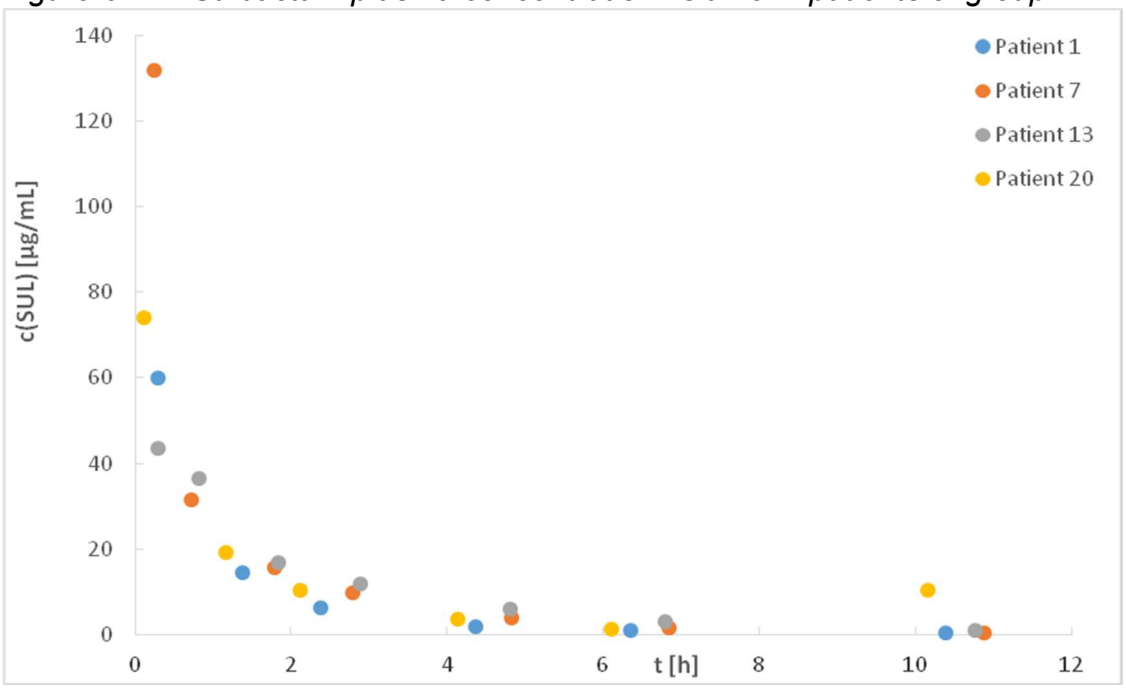


Figure 6-12 Ampicillin plasma concentration vs time in patients of group 3.

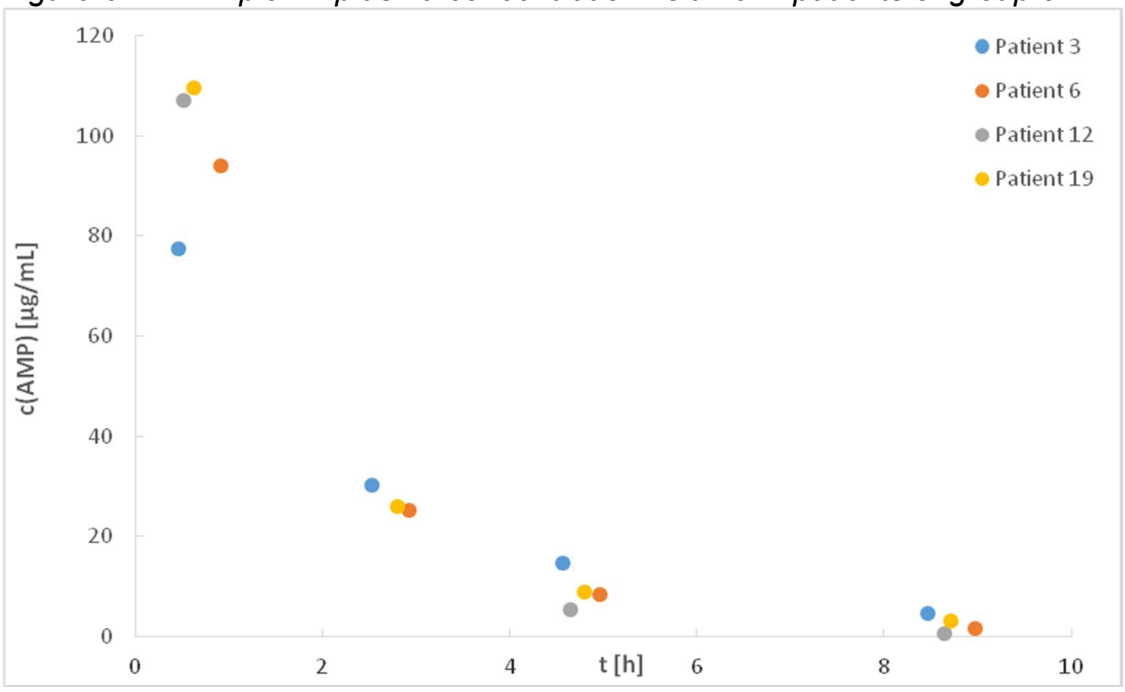


Figure 6-13 Sulbactam plasma concentration vs time in patients of group 3.

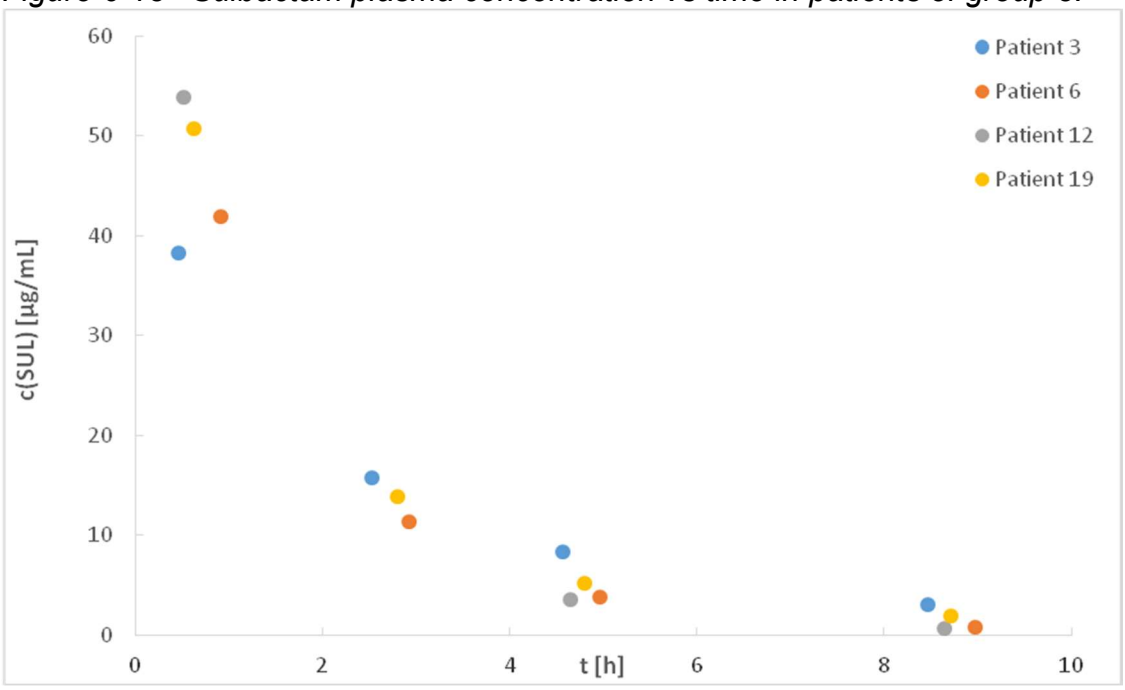


Figure 6-14 Ampicillin plasma concentration vs time in patients of group 4.

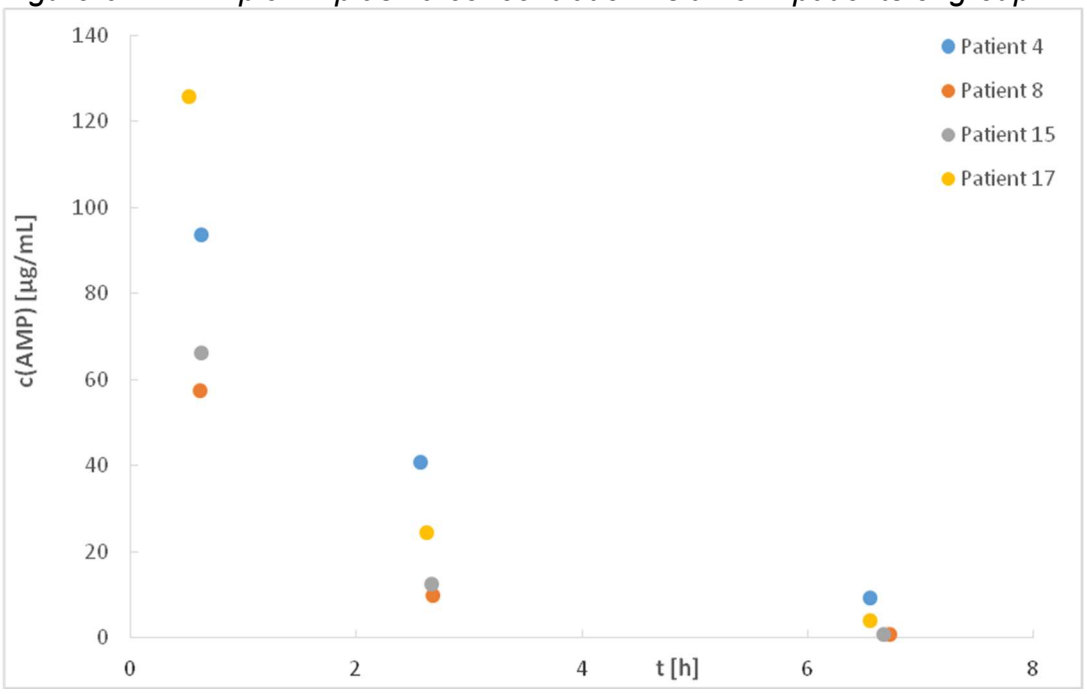


Figure 6-15 Sulbactam plasma concentration vs time in patients of group 4.

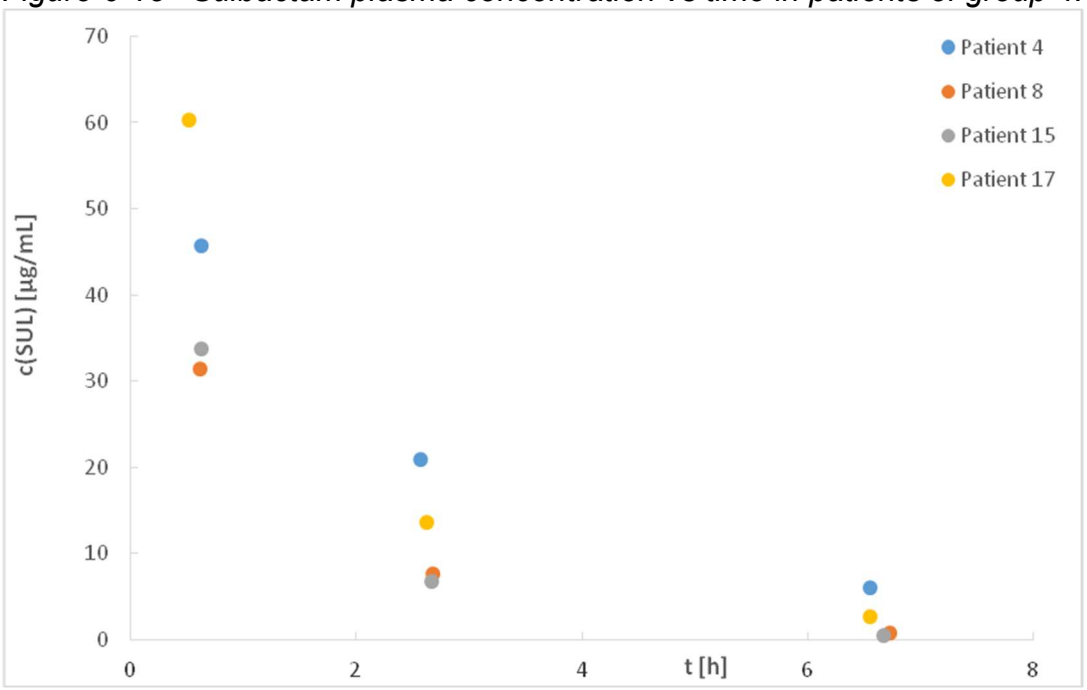


Figure 6-16 Ampicillin plasma concentration vs time in patients of group 5.

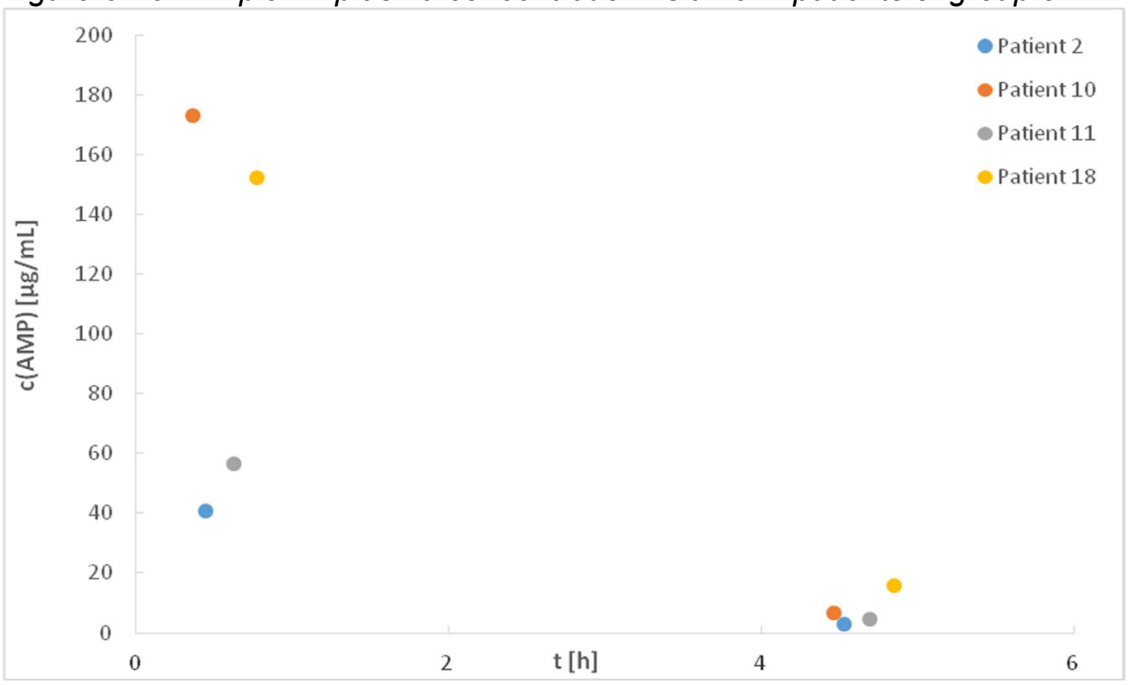
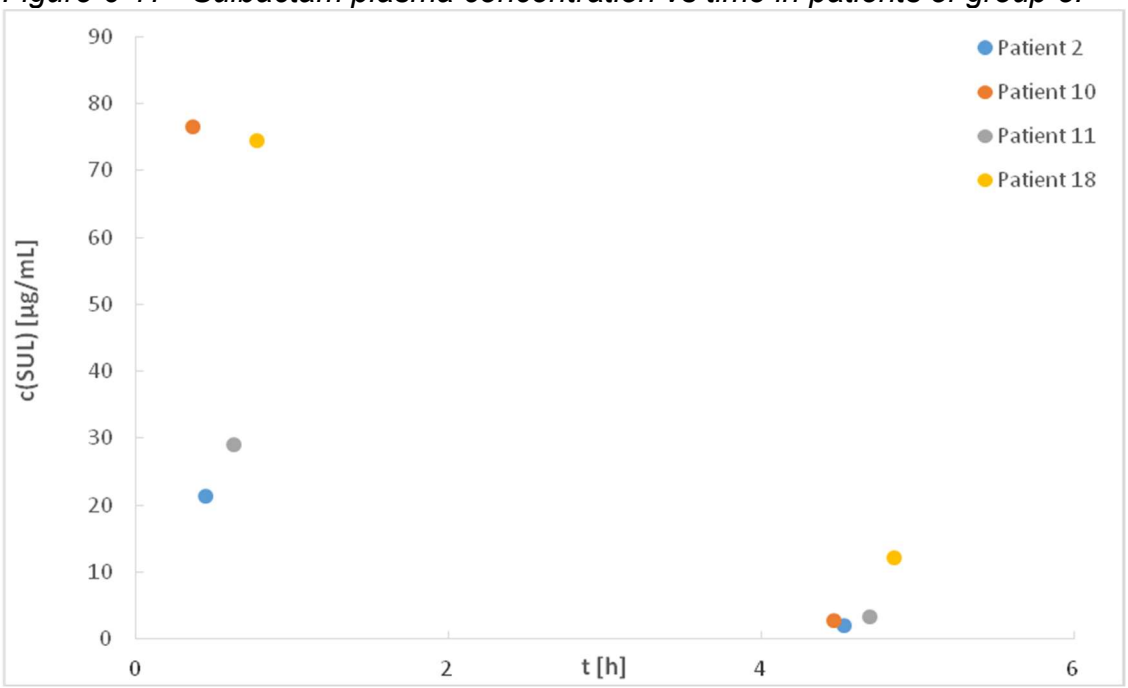


Figure 6-17 Sulbactam plasma concentration vs time in patients of group 5.



6.3.3. Pharmacokinetic parameters of ampicillin and sulbactam in plasma

The mean ± SD peak plasma levels of ampicillin and sulbactam of all patients were 119.3 ± 65.0 (range 40.6 - 285.8) and 57.2 ± 28.5 µg/mL (range 21.3 - 132.0). The mean ± SD time elapsed between start of infusion and the time of the first sampling past start of infusion was 0.49 ± 0.20 h (range 0.23 - 0.92). Mean ± SD infusion duration was 0.23 ± 0.06 h (range 0.13 - 0.35). Hence, the wide distribution of the peak concentrations can partly be explained by the different time intervals between the start of infusion and the time of blood sampling, and by the different duration of the infusions.

The determination of the elimination rate constant ke of ampicillin (a) and sulbactam (b) by least squares regression analysis resulted in objectively reliable results, as can be seen by the graphical representations in Figure 13-1 to 13-32 in the appendix. The resulting mean ± SD terminal half-life of ampicillin and sulbactam was 1.60 ± 0.37 (range 1.05 - 2.23) and 1.70 ± 0.42 h (range 1.12 - 2.53). Half-life of ampicillin and sulbactam was in good correlation with creatinine clearance, showing correlation coefficients (r) of 0.729 (p=0.003) and 0.699 (p=0.005). A graphical representation of the correlation of the half-life of ampicillin and sulbactam with creatinine clearance is shown in Figure 6-18 and 6-19. The attempt to correlate the half-life of ampicillin and sulbactam with serum creatinine levels resulted in poorer correlation for ampicillin with r = 0.661 (p=0.010) and slightly better correlation for sulbactam with r = 0.729 (p=0.003).

The application of the linear trapezoidal rule for the determination of the total area under the concentration-time curve ($AUC_{0-\infty}$) resulted in mean ± SD $AUC_{0-\infty}$ estimates of 208.6 ± 65.4 µg*h/mL (range 111.1 – 306.1) for ampicillin and 106.3 ± 31.3 µg*h/mL (62.9 – 151.7) for sulbactam. As might be expected, the $AUC_{0-\infty}$ of ampicillin and sulbactam of patient 16, who received accidentally a second dose of ampicillin and sulbactam, was about twice as high as the mean (478.1 and 235.9 µg*h/mL).

Mean ± SD clearance (CL) and volume of distribution (Vd) of ampicillin and sulbactam were 10.7 ± 3.9 (range 6.5 - 18.0) and 10.3 ± 3.3 L/h (range 6.6 - 15.9), respectively, and 23.9 ± 7.9 (range 12.9 - 41.3) and 24.3 ± 6.8 L (range 14.9 - 38.9), respectively. The correlation of ampicillin and sulbactam clearances with creatinine

clearance resulted in correlation coefficients (r) of 0.610 (p=0.021) and 0.502 (p=0.068). Correlations of ampicillin and sulbactam clearance with serum creatinine showed even poorer r of 0.252 (p=0.385) and 0.257 (p=0.375). The attempt to correlate the volume of distribution of ampicillin and sulbactam with different demographical parameters also failed. The correlation coefficients for the volume of distribution of ampicillin with weight, body mass index, lean body mass and height were r = 0.406 (p=0.150), r = 0.274 (p=0.344), r = 0.457 (p=0.100) and r = 0.406 (p=0.150), respectively. The correlation coefficients for the volume of distribution of sulbactam with these demographical parameters were r = 0.353 (p=0.215), r = 0.244 (p=0.400), r = 0.406 (p=0.149) and r = 0.353 (p=0.215), respectively. In summary, no demographical parameters were found, which showed good correlation with ampicillin or sulbactam clearance or volume of distribution. Graphical representations of the correlation of ampicillin (a) and sulbactam (b) clearance and volume of distribution with demographical data is provided in Figure 13-33 to 13-44 in the appendix.

An overview of the resulting pharmacokinetic parameters of ampicillin and sulbactam in plasma is shown in Table 6-2 and 6-3.

Table 6-2 Pharmacokinetic parameters in plasma for ampicillin.

		Cmax [µg/mL]	ke [/h]	$t_{1/2}$ [h]	$AUC_{0-\infty}$ [µg*h/mL]	CL [L/h]	CL [mL/min]	Vd [L]
Group 1	Patient 5	173.6	0.613	1.13	144.80	13.81	230.20	22.52
Group 1	Patient 9	93.2	0.391	1.77	123.83	16.15	269.18	41.27
Group 1	Patient 14	241.1	0.507	1.37	306.14	6.53	108.88	12.87
Group 1	Patient 16*	144.1	0.437	1.59	478.14	8.37	139.43	19.14
Group 2	Patient 1	122.2	0.406	1.71	145.16	13.78	229.63	33.91
Group 2	Patient 7	285.8	0.425	1.63	237.71	8.41	140.23	19.81
Group 2	Patient 13	78.3	0.324	2.14	213.42	9.37	156.19	28.92
Group 2	Patient 20**	164.6	0.570	1.22	283.52	7.05	117.57	12.37
Group 3	Patient 3	77.5	0.311	2.23	227.25	8.80	146.68	28.30
Group 3	Patient 6	94.1	0.443	1.56	220.62	9.07	151.09	20.46
Group 3	Patient 12	107.1	0.536	1.29	272.72	7.33	122.23	13.68
Group 3	Patient 19	109.6	0.347	1.99	248.44	8.05	134.17	23.17
Group 4	Patient 4	93.7	0.372	1.86	284.99	7.02	116.97	18.85
Group 4	Patient 8	57.6	0.597	1.16	111.05	18.01	300.17	30.18
Group 4	Patient 15	66.4	0.662	1.05	129.85	15.40	256.70	23.28
Group 4	Patient 17	125.7	0.460	1.51	254.95	7.84	130.75	17.05
Group 5	Patient 2	40.6	-	-	-	-	-	-
Group 5	Patient 10	173.1	-	-	-	-	-	-
Group 5	Patient 11	56.4	-	-	-	-	-	-
Group 5	Patient 18	152.2	-	-	-	-	-	-
Mean		**119.3**	**0.457**	**1.60**	**208.6**	**10.7**	**178.1**	**23.9**
SD		**65.0**	**0.111**	**0.37**	**65.4**	**3.9**	**64.6**	**7.9**

* Patient received a 2nd infusion ampicillin/sulbactam starting 33min past start of first infusion and 55min before bone resection; PK parameters excluded from calculation of the means
** Infusion ongoing; PK parameters excluded from calculation of the means

Table 6-3 Pharmacokinetic parameters in plasma for sulbactam.

		Cmax [µg/mL]	ke [/h]	$t_{1/2}$ [h]	$AUC_{0-\infty}$ [µg*h/mL]	CL [L/h]	CL [mL/min]	Vd [L]
Group 1	Patient 5	83.2	0.586	1.18	80.12	12.48	208.0	21.30
Group 1	Patient 9	46.7	0.409	1.70	62.92	15.89	264.9	38.86
Group 1	Patient 14	107.0	0.471	1.47	142.27	7.03	117.1	14.92
Group 1	Patient 16*	63.8	0.404	1.72	235.94	8.48	141.3	21.01
Group 2	Patient 1	59.9	0.401	1.73	72.86	13.73	228.8	34.23
Group 2	Patient 7	132.0	0.410	1.69	117.31	8.52	142.1	20.79
Group 2	Patient 13	43.4	0.329	2.11	105.35	9.49	158.2	28.85
Group 2	Patient 20**	74.1	0.519	1.34	130.26	7.68	127.9	14.80
Group 3	Patient 3	38.3	0.274	2.53	122.45	8.17	136.1	29.80
Group 3	Patient 6	41.9	0.442	1.57	98.70	10.13	168.9	22.92
Group 3	Patient 12	53.9	0.452	1.53	142.44	7.02	117.0	15.53
Group 3	Patient 19	50.7	0.326	2.12	124.91	8.01	133.4	24.56
Group 4	Patient 4	45.7	0.314	2.21	151.66	6.59	109.9	21.00
Group 4	Patient 8	31.4	0.575	1.20	68.14	14.67	244.6	25.52
Group 4	Patient 15	33.7	0.621	1.12	67.60	14.79	246.6	23.82
Group 4	Patient 17	60.3	0.415	1.67	132.02	7.57	126.2	18.25
Group 5	Patient 2	21.3	-	-	-	-	-	-
Group 5	Patient 10	76.6	-	-	-	-	-	-
Group 5	Patient 11	29.0	-	-	-	-	-	-
Group 5	Patient 18	74.4	-	-	-	-	-	-
Mean		**57.2**	**0.430**	**1.70**	**106.3**	**10.3**	**171.6**	**24.3**
SD		**28.5**	**0.106**	**0.42**	**31.3**	**3.3**	**55.3**	**6.8**

* Patient received a 2nd infusion ampicillin/sulbactam starting 33min past start of first infusion and 55min before bone resection; PK parameters excluded from calculation of the means
** Infusion ongoing; PK parameters excluded from calculation of the means

Figure 6-18 Correlation plot of ampicillin half-life vs. creatinine clearance.

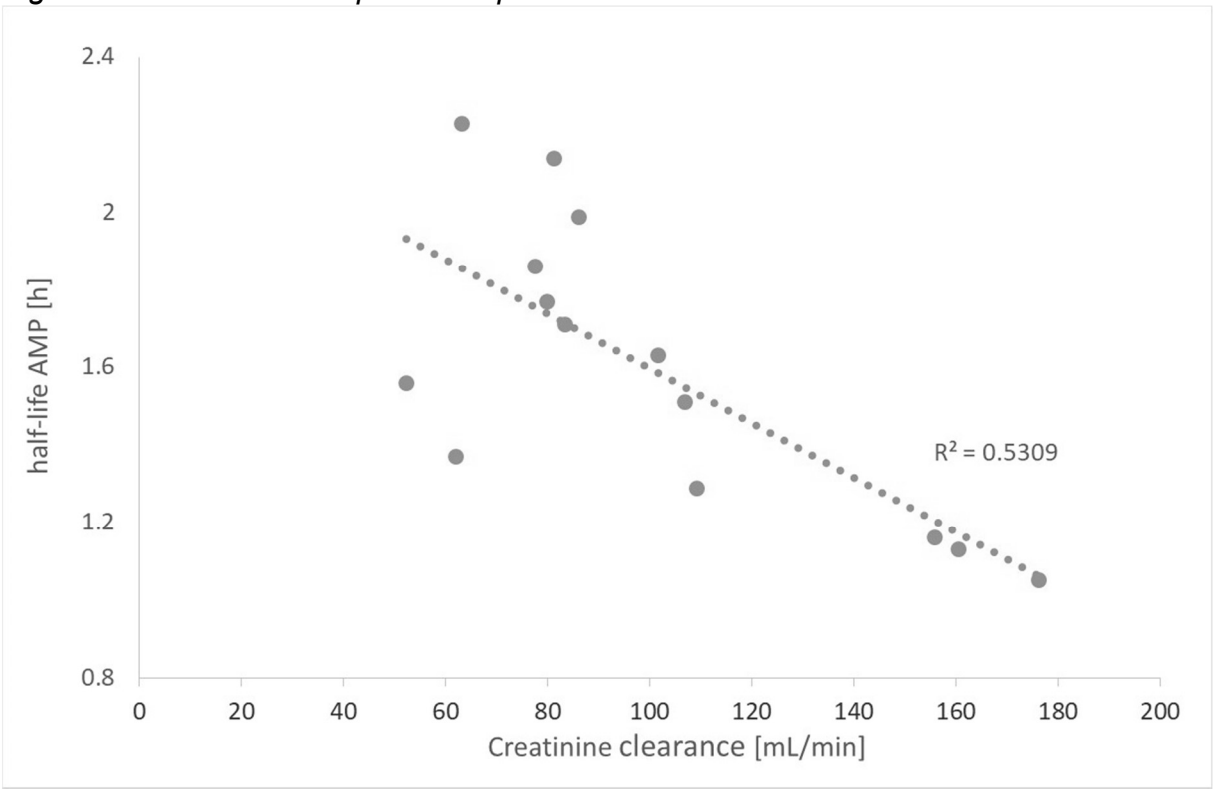
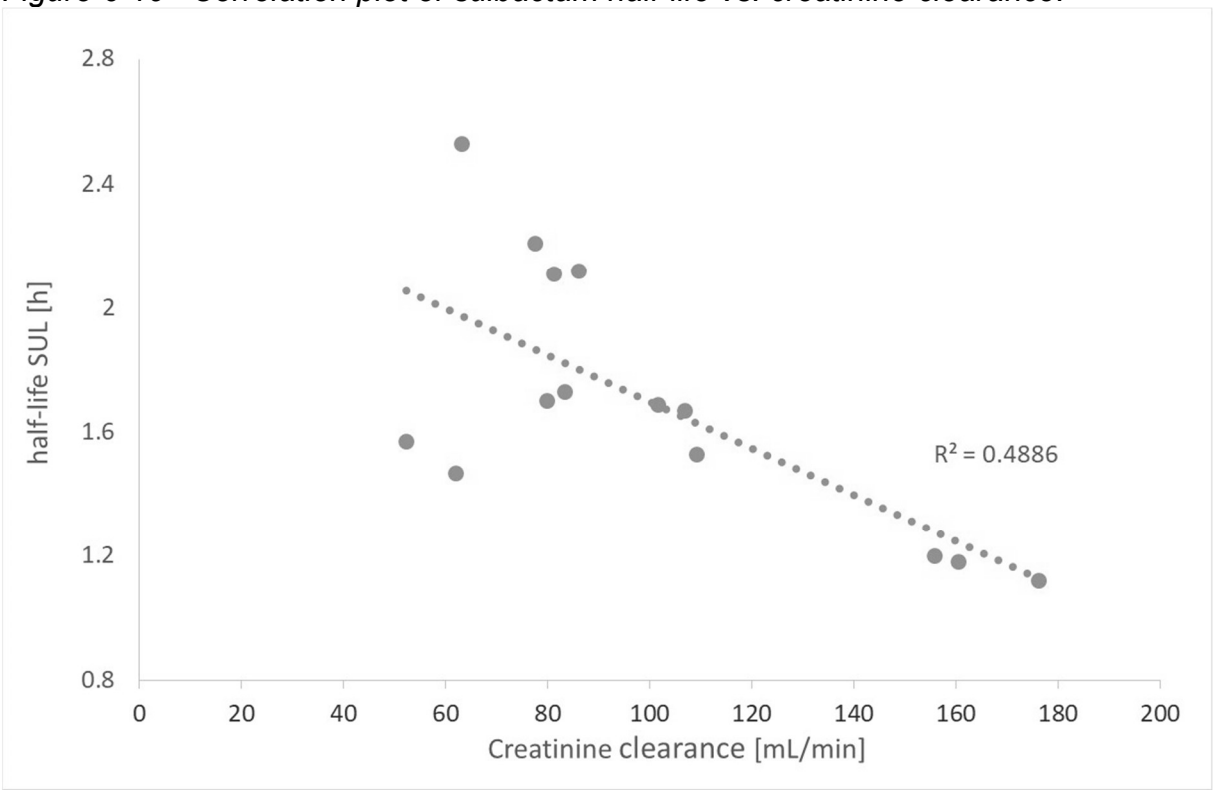


Figure 6-19 Correlation plot of sulbactam half-life vs. creatinine clearance.



6.3.4. Bone penetration of ampicillin and sulbactam

The mean ± SD time between the start of the infusion and the time of bone resection was 0.74 ± 0.35 h (range 0.30 to 1.43). Mean ± SD concentrations of ampicillin in cortical and cancellous bone were 6.60 ± 4.22 (range 2.01 - 17.85) and 10.15 ± 7.40 µg/g (range 0.07 - 23.26), resulting in bone penetration ratios (BPR) in cortical and cancellous bone of 9.1 ± 5.7 (range 3.1 - 23.3) and 16.2 ± 16.9 % (range 0.1 - 71.3). For sulbactam, mean ± SD concentrations in cortical and cancellous bone were 3.91 ± 2.52 (range 1.16 - 10.48) and 5.73 ± 4.20 µg/g (range 0.04 - 12.59), resulting in BPR in cortical and cancellous bone of 10.6 ± 6.3 (range 3.6 - 23.7) and 17.5 ± 16.1 % (range 0.1 - 63.6).

An overview of the plasma and bone concentrations at the time of bone resection and the degree of penetration of ampicillin and sulbactam in bone is shown in Table 6-4 and 6-5. A graphical representation of the concentrations of ampicillin and sulbactam in plasma, cortical and cancellous bone at the time of bone resection is shown in Figure 6-20 and 6-21. In addition, a graphical representation of the BPR of ampicillin and sulbactam in cortical and cancellous bone at the time of bone resection is shown in Figure 6-22 and 6-23.

Ampicillin and sulbactam concentrations in cortical vs. cancellous bone showed poor correlation, with correlation coefficients (r) of 0.102 (p=0.688) and 0.053 (p=0.835). However, the BPR of ampicillin and sulbactam in cortical vs. cancellous bone showed r of 0.586 (p=0.011) and 0.446 (p=0.064). As a result, the BPR, but not the concentrations in cortical vs. cancellous bone of both substances seem to be correlated.

The attempt to correlate the time elapsed between the start of the infusion and the time of bone resection (Δt) vs. the concentrations of ampicillin and sulbactam in cortical bone resulted in r of 0.318 (p=0.199) and 0.334 (p=0.175). For cancellous bone, r was 0.318 (p=0.199) and r = 0.307 (p=0.215), respectively. Therefore, ampicillin and sulbactam concentrations in cortical and cancellous bone were considered not to be correlated with Δt.

The attempt to correlate Δt with the BPR of ampicillin and sulbactam in cortical bone resulted in r of 0.284 (p=0.253) and 0.210 (p=0.404), respectively. For cancellous bone, the resulting correlation coefficients (r) for ampicillin and sulbactam were 0.699

(p=0.001) and 0.719 (p=0.001), respectively. In conclusion, the BPR of both substances in cancellous bone, but not in cortical bone is significantly correlated with Δt.

Graphical representations of the correlation attempts described in this section are provided in Figure 13-45 to 13-56 in the appendix.

Table 6-4 Bone penetration of ampicillin.

		Δt [h]	c(Plasma) [µg/mL]	c(cort. bone) [µg/g]	c(canc. bone) [µg/g]	BPR (cort. bone)	BPR (canc. bone)
Group 1	Patient 5	1.42	21.80	5.07	15.54	23.3%	71.3%
Group 1	Patient 9	1.40	22.23	2.01	5.31	9.0%	23.9%
Group 1	Patient 14	1.43	71.32	5.76	23.26	8.1%	32.6%
Group 1	Patient 16*	1.47/0.92	119.30	11.98	4.69	10.0%	3.9%
Group 2	Patient 1	0.30	122.20	6.18	2.21	5.1%	1.8%
Group 2	Patient 7	0.72	65.97	9.40	21.75	14.3%	33.0%
Group 2	Patient 13	0.82	75.41	5.43	7.95	7.2%	10.5%
Group 2	Patient 20**	0.12	164.60	1.24	0.57	0.8%	0.3%
Group 3	Patient 3	0.45	77.46	8.39	0.07	10.8%	0.1%
Group 3	Patient 6	0.92	94.05	5.29	6.67	5.6%	7.1%
Group 3	Patient 12	0.52	107.10	3.88	20.89	3.6%	19.5%
Group 3	Patient 19	0.63	109.60	4.62	4.14	4.2%	3.8%
Group 4	Patient 4	0.63	93.73	17.85	3.96	19.1%	4.2%
Group 4	Patient 8	0.62	57.61	6.12	9.39	10.6%	16.3%
Group 4	Patient 15	0.63	66.39	4.20	12.57	6.3%	18.9%
Group 4	Patient 17	0.52	125.70	3.95	2.60	3.1%	2.1%
Group 5	Patient 2	0.45	40.59	6.36	5.72	15.7%	14.1%
Group 5	Patient 10	0.37	173.10	16.28	19.04	9.4%	11.0%
Group 5	Patient 11	0.63	56.40	2.27	6.50	4.0%	11.5%
Group 5	Patient 18	0.78	152.20	5.72	15.15	3.8%	10.0%
Mean		**0.74**	**85.16**	**6.60**	**10.15**	**9.1%**	**16.2%**
SD		**0.35**	**41.37**	**4.22**	**7.40**	**5.7%**	**16.9%**

* Patient received a 2nd infusion ampicillin/sulbactam starting 33min past start of first infusion and 55min before bone resection; PK parameters excluded from calculation of the means
** Infusion ongoing; PK parameters excluded from calculation of the means

Table 6-5 Bone penetration of sulbactam.

		Δt [h]	c(Plasma) [µg/mL]	c(cort. bone) [µg/g]	c(canc. bone) [µg/g]	BPR (cort. bone)	BPR (canc. bone)
Group 1	Patient 5	1.42	14.0	3.32	8.90	23.7%	63.6%
Group 1	Patient 9	1.40	12.0	1.16	2.97	9.7%	24.8%
Group 1	Patient 14	1.43	31.1	3.27	12.59	10.5%	40.5%
Group 1	Patient 16*	1.47 / 0.92	47.5	7.49	2.69	15.8%	5.7%
Group 2	Patient 1	0.30	59.9	4.31	1.25	7.2%	2.1%
Group 2	Patient 7	0.72	31.4	5.64	11.64	18.0%	37.1%
Group 2	Patient 13	0.82	36.4	3.10	4.32	8.5%	11.9%
Group 2	Patient 20**	0.12	74.1	0.68	0.29	0.9%	0.4%
Group 3	Patient 3	0.45	38.3	5.74	0.04	15.0%	0.1%
Group 3	Patient 6	0.92	41.9	2.68	3.04	6.4%	7.3%
Group 3	Patient 12	0.52	53.9	2.21	11.57	4.1%	21.5%
Group 3	Patient 19	0.63	50.7	2.81	2.42	5.5%	4.8%
Group 4	Patient 4	0.63	45.7	10.48	2.14	22.9%	4.7%
Group 4	Patient 8	0.62	31.4	3.64	5.86	11.6%	18.7%
Group 4	Patient 15	0.63	33.7	2.24	6.60	6.6%	19.6%
Group 4	Patient 17	0.52	60.3	2.15	1.42	3.6%	2.4%
Group 5	Patient 2	0.45	21.3	3.58	3.14	16.8%	14.7%
Group 5	Patient 10	0.37	76.6	9.42	10.58	12.3%	13.8%
Group 5	Patient 11	0.63	29.0	1.35	3.78	4.7%	13.0%
Group 5	Patient 18	0.78	74.4	3.32	10.95	4.5%	14.7%
Mean		**0.74**	**41.22**	**3.91**	**5.73**	**10.6%**	**17.1%**
SD		**0.35**	**18.57**	**2.52**	**4.20**	**6.3%**	**16.5%**

* Patient received a 2nd infusion ampicillin/sulbactam starting 33min past start of first infusion and 55min before bone resection; PK parameters excluded from calculation of the means
** Infusion ongoing; PK parameters excluded from calculation of the means

Figure 6-20 Log-linear plot of ampicillin plasma and bone concentrations over time.

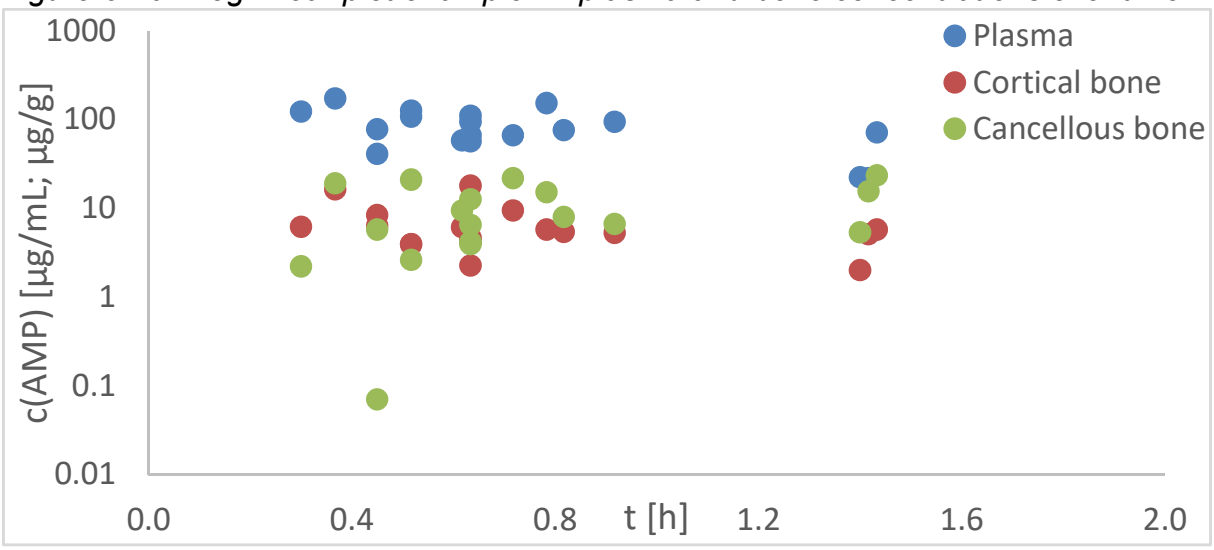


Figure 6-21 Log-linear plot of sulbactam plasma and bone concentrations over time.

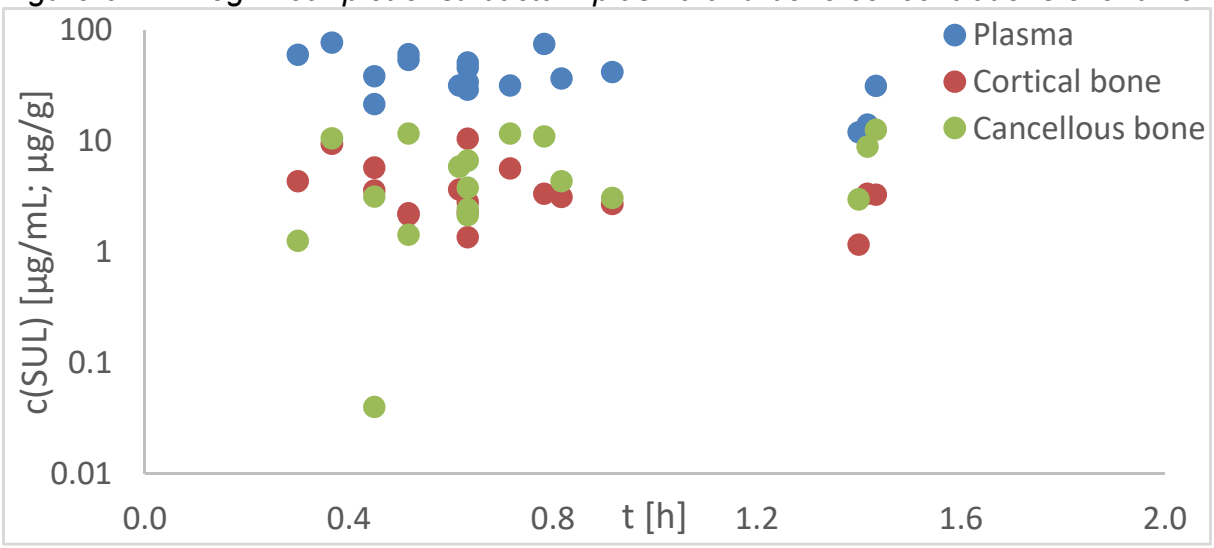


Figure 6-22 Bone penetration of ampicillin over time.

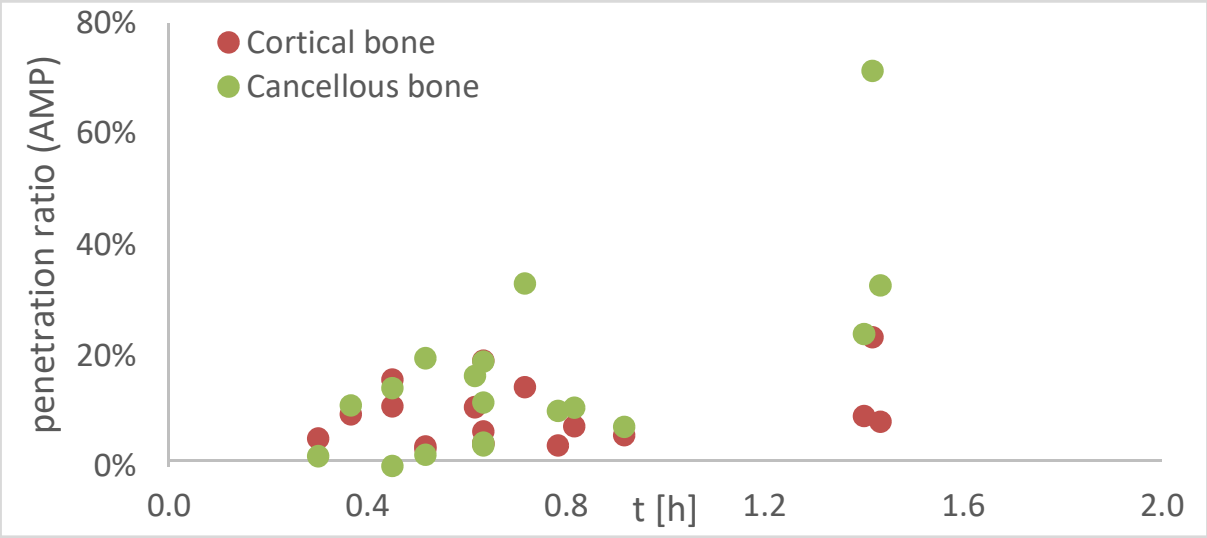
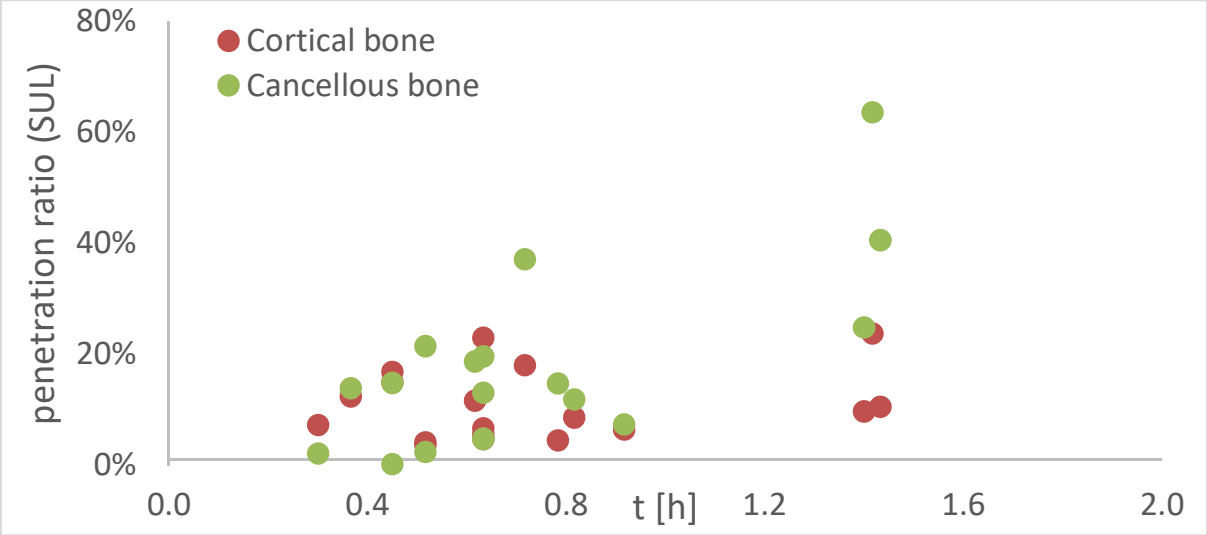


Figure 6-23 Bone penetration of sulbactam over time.



6.3.5. Microbial outcome

No surgical site infections occurred in this study.

6.4. Discussion

This study investigated the pharmacokinetics of ampicillin and sulbactam in plasma and bone in patients undergoing total hip replacement surgery.

Our first objective was to determine the pharmacokinetics of both substances in plasma. Due to the underlying study protocol, a limited number of plasma samples was available in patients of group 4 and group 5. While the visual check of the elimination rate constant (Figure 13-25 to 13-32 in the appendix) and the resulting pharmacokinetic parameters of group 4 seemed reasonable, patients of group 5 were excluded from the pharmacokinetic analysis due to the insufficient number of plasma samples. In addition, two of the remaining 16 patients received accidently a second dose of ampicillin and sulbactam and were therefore excluded from the calculation of the means of the study population.

The resulting mean ± SD $AUC_{0-\infty}$, CL and Vd in plasma was 208.6 ± 65.4 µg*h/mL, 178.1 ± 64.6 mL/min, and 23.9 ± 7.9 L for ampicillin and 106.3 ± 31.3 µg*h/mL, 171.6 ± 55.3 mL/min, and 24.3 ± 6.8 L for sulbactam, respectively. These results were in good agreement with literature data of elderly healthy volunteers who were treated with the same dose of ampicillin and sulbactam (2000 mg / 1000 mg). For instance, Meyers et al.[190] reported ampicillin $AUC_{0-\infty}$ of 182.15 ± 57.79 µg*h/mL, CL of 198.02 ± 55.60 mL/min and Vd of 26.33 ± 8.75 L, in the subgroup of elderly healthy volunteers. The corresponding values for sulbactam were: $AUC_{0-\infty}$, 110.37 ± 32.70 µg*h/mL; CL, 162.69 ± 46.21 mL/min; and Vd, 23.54 ± 7.71 L.

It is a noteworthy finding of our study, that the renal function, represented by the creatinine clearance (estimated by the Cockcroft and Gault formula), correlated significantly better with half-life of ampicillin and sulbactam (r = 0.729 and 0.699), than with ampicillin and sulbactam clearance (r = 0.610 and 0.502).

The second objective of our study was to determine the concentrations of ampicillin and sulbactam in the two main bone tissues - cortical bone and cancellous bone - during total hip replacement surgery. This data is particularly relevant, as the capacity of an antibiotic to penetrate tissues, and in particular bone, is an important predictive parameter for success in treating and preventing bone infections. However, information on the bone penetration of ampicillin co-administered with sulbactam, particularly when administered as antibiotic prophylaxis in the setting of major

orthopedic surgery, is limited. Reasons are the limited number of studies, which have investigated bone concentrations of ampicillin co-administered with sulbactam and the conflicting results of these studies.

Dehne et al. studied bone and serum concentrations of ampicillin and sulbactam in the setting of major orthopedic surgery using blood saving techniques[191]. The resulting bone penetration ratios of ampicillin and sulbactam one hour after administration were 44.2 for ampicillin and 58.3 % for sulbactam. Penetration ratios increased to 71.4 and 70.6 %, four hours after administration. In contrast, Wildfeuer et al. reported bone concentrations of ampicillin and sulbactam of 21.8 ± 10.5 (n=9) and 4.9 ± 2.2 (n=9) mg/kg in samples collected 0.25 h past infusion[192]. The corresponding serum concentrations of ampicillin and sulbactam were 107.7 ± 48.5 (n=40) and 28.6 ± 16.2 (n=40) mg/L, which resulted in bone penetration ratios of 20.2 and 17.1 %. Other studies on the bone penetration of ampicillin and sulbactam were not in the setting of orthopedic surgery. The most recent one of Heibel et al. studied bone concentrations of ampicillin and sulbactam after resection of the irradiated mandible after oral squamous cell cancer[193]. The resulting bone penetration ratios of ampicillin and sulbactam were only 4.4 and 1.9 %. Warnke et al. studied the concentrations of ampicillin and sulbactam in bone of the vertebral body in patients undergoing spinal microneurosurgical procedures. The resulting bone penetration ratios for ampicillin and sulbactam in this study were 11.8 and 23.0 %[185]. Finally, Wildfeuer et al. studied the concentrations of ampicillin and sulbactam in sternal bone in patients undergoing heart surgery[194]. The resulting bone penetration ratios for ampicillin and sulbactam were 26.5 and 28.1 %.

The results of our study show mean ± SD bone penetration ratios for ampicillin into cortical and cancellous bone of 9.1 ± 5.7 and 16.2 ± 16.9 %. Penetration ratios for sulbactam into cortical and cancellous bone were 10.6 ± 6.3 and 17.1 ± 16.5 %. This data is in the same order of magnitude as the bone penetration ratios reported in the studies described above, with the exception of the results reported by Dehne et al. As already described by Landersdorfer et al., this could be due to blood saving techniques, used in this study, which resulted in lower plasma concentrations and therefore higher penetration ratios of ampicillin and sulbactam[195]. However, despite using a validated, very efficient and reproducible method for the determination of ampicillin and

sulbactam in human bone, the individual results of the concentrations and bone penetration rations of ampicillin and sulbactam in cortical and cancellous bone showed a wide variability in our study. One reason for the variability in bone concentrations might be the different composition of bone tissue from patient to patient. For instance, the specimens of cortical bone differed much in thickness and the specimens of cancellous bone differed much in moisture, color and adhering blood from patient to patient.

An additional factor for the varying bone penetration ratios was the time elapsed between drug administration and bone resection. These two variables were significantly correlated in cancellous, but not in cortical bone. As a result, a sufficient period of time between the administration of ampicillin/sulbactam and bone resection seems to be necessary to obtain adequate concentrations in cancellous bone.

In conclusion, our study could not demonstrate sufficient concentrations of ampicillin and sulbactam for anti-infective prophylaxis in all patients. However, it is noteworthy that no surgical site infection occurred in this study. Additional studies in the setting of total hip replacement surgery are needed, to determine whether this combination is superior to the standard prophylaxis with cefazolin.

7. Azathioprine-induced reversible EBV-associated Hodgkin-like lymphoma after immunosuppressive therapy for autoimmune hepatitis

Munz M, Pretscher D, Wilhelm M, Holzgrabe U, Sörgel F, Birkmann J: Azathioprine-induced reversible EBV-associated Hodgkin-like lymphoma after immunosuppressive therapy for autoimmune hepatitis. Int J Clin Pharmacol Ther. 2018;56:142-147.

7.1. Introduction

Immunosuppression is a risk factor for the development of different malignancies, e.g., skin and hematologic tumors. There is a well-established relationship between immunosuppression- or stem cell transplantation-induced T cell dysfunction and reactivation of Epstein-Barr virus (EBV). The clearest connection between EBV reactivation and development of lymphoma is seen in solid organ transplantation and in recipients of allogenic hematopoietic stem cell transplantation.

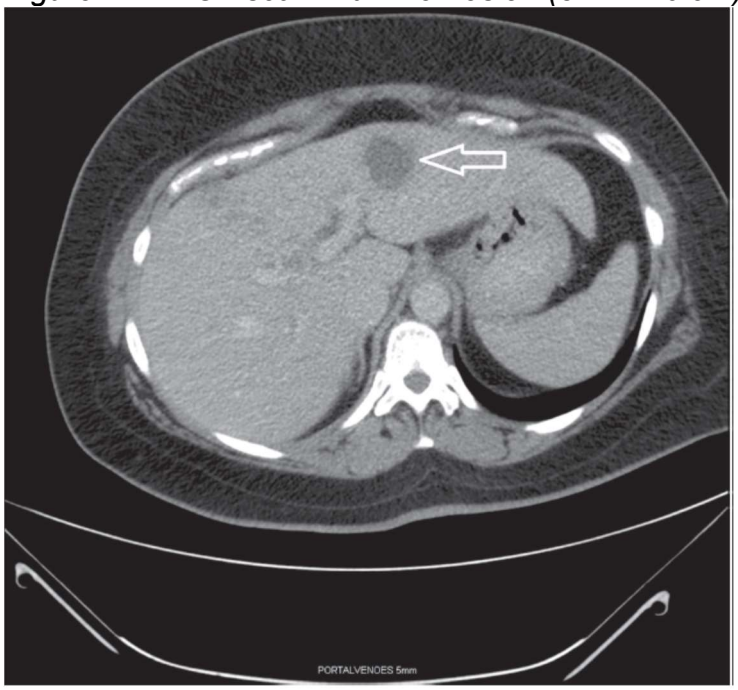
EBV is a member of the herpes virus family that establishes a lifelong persistence in B lymphocytes after infection. It is estimated that more than 90% of the adult population worldwide are infected with this virus[196–198], but in physiologic circumstances, the inherent propensity of EBV to induce B cell proliferation is counterbalanced by complex immunologic interactions that maintain the overall number of EBV-infected B cells at a very low level[197,199]. A crucial role in this immunological reactions to control EBV-infected B cells is played by T cells, especially cytotoxic CD8+ T cells, which eliminate proliferating infected B cells[200,201]. EBV can immortalize the infected B cell and is also able to drive the infected B cell from the resting state into continuous proliferation. In the absence of T cell control, this can result in lymphoma[202]. The purine antimetabolite azathioprine is an oral immunosuppressive drug that inhibits de novo purine synthesis after cleavage to 6-mercaptopurine, which in turn is converted to further metabolites[203]. The resulting reduction in intracellular purine synthesis leads to decreased numbers of circulating B and T lymphocytes[204,205], reduced immunoglobulin synthesis[205], and diminished interleukin-2 (IL-2) secretion[206,207]. It is therefore a well-established hypothesis that dysregulation or suppression of T cell function by immunosuppressive treatment with azathioprine is a strong risk factor for the reactivation of EBV and therefore for the

development of EBV-associated lymphoproliferative disorder (LPD). Patients in whom the lymphoma disappeared after discontinuation of immunosuppressive therapy emphasize this hypothesis[208,209].

7.2. Case Report

A 38-year-old woman with a 23-year history of systemic lupus erythematosus and a 26-month history of autoimmune hepatitis type 1 treated with azathioprine (50 mg/d) presented to her family doctor with abdominal pain. An ultrasound of the liver revealed several liver lesions. Before admission to the department of gastroenterology for further workup, a CT scan was performed, which showed pulmonary lesions, a 3.2 × 2.4 cm mediastinal mass, several smaller liver lesions and one liver lesion up to 3.2 × 2.6 cm (Figure 7-1).

Figure 7-1 CT scan with liver lesion (3.2 x 2.6 cm) before admission.



Upon admission, the laboratory values of the patient showed a mild anemia with 3.4 erythrocytes/pL (normal: 4.2 - 5.4 erythrocytes/pL). Her leucocytes were decreased to 2.7/nL (normal: 4.0 - 10.0 leucocytes/nL). The liver enzymes gamma-GT and ASAT were slightly above normal with values of 58 U/L (normal: < 40 U/L) and 45 (normal: <

35 U/L), LDH and CRP were elevated to 278 U/L and 4.9 mg/dL (normal: < 250 U/L and < 0.5 mg/dL), respectively.

Due to progressive leukopenia of down to 1.6 leucocytes/nL, the immunosuppressive therapy with azathioprine was withdrawn early after admission.

Further workup included an MRI scan of the liver with MRCP (magnetic resonance cholangiopancreatography), which showed several few-millimeter small foci of the liver with a diffuse distribution and one larger lesion with ~ 4.5 cm in diameter. Distinction between a neoplastic and an inflammatory process could not accurately be made. Therefore, an ultrasound-controlled core needle biopsy of this liver lesion was performed.

The initial histological examination revealed granulomatous inflammation with vasculitic changes and necrosis. Additionally, EBV-positive, B-lymphatic Hodgkin-like lymphoma cells were seen that had similarity to Hodgkin and Reed/Sternberg cells. Due to this extraordinary histological finding and the patient's history of autoimmune disease, the biopsy specimen was referred to a specialized lymphoma pathology center in Würzburg, Germany.

After that, the patient was referred to our department of hematology and oncology for further workup and therapy. We additionally conducted a bone marrow biopsy, which revealed a lymphoid-acting mixed infiltrate which presented CD15+, CD30+, and PAX-5+ cells by immunohistochemical staining. These cells represented ~ 15% of bone marrow cells.

Regarding the immunosuppressive therapy with azathioprine, we initiated an extended serological testing as shown in Table 7-1. Most noticeable were high EBV DNA titers (57,000 copies/mL) indicating an acute EBV infection. This raised the strong suspicion of an immunosuppression-associated LPD.

Table 7-1 Serological findings.

	result	**unit**	**normal**
Beta-2 microglobulin	4.5	mg/L	1.2-2.5
Cryoglobulins	not detected		
Antinuclear antibodies (ANA) [indirect immunofluorescence]	>1:5120	titer	>1:80
Extractable nuclear antigens (ENA) [ELISA]	positive	-	-
- SS-A/Ro	highly positive	-	-
- SS-B/La	negative	-	-

- Sm	negative	-	-
- RNP	negative	-	-
- Scl-70	negative	-	-
- Jo-1	negative	-	-
dsDNA [ELISA]	<20	U/mL	<20
anti-neutrophil cytoplasmic antibodies (ANCA) [indirect immunofluorescence]			
- c-ANCA	negative	-	-
- p-ANCA	negative	-	-
anti-smooth muscle antibodies (ASMA) [indirect immunofluorescence]	1:80	titer	<1:40
Hepatitis B			
- Hepatitis B (s) Antigen [CMIA]	negative	-	-
- Hepatitis B (core) - AK [CMIA]	negative	-	-
Hepatitis C			
- Hepatitis C - AK [CMIA]	negative	-	-
HIV			
- HIV 1/2 Ag / AK [CMIA]	negative	-	-
EBV			
- EBV-DNA quant. [real-time-PCR]	57000	copies/mL	-

We initiated a treatment with 100 mg of prednisolone for four days, which improved the patient's condition regarding her abdominal pain. Furthermore, the patient received 100 mg of aspirin, 40 mg of pantoprazole, and 5 mg of ramipril daily.

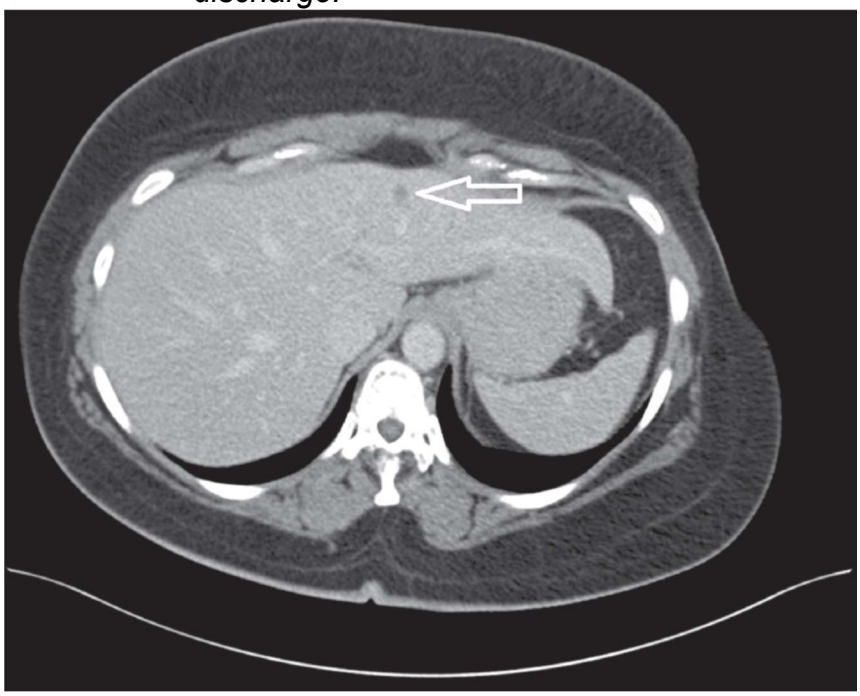
A few days later, we received the diagnosis from the specialized lymphoma pathology center, which confirmed our diagnosis of an EBV-associated Hodgkin-like lymphoma: There were relatively numerous, eosinophilic lymphocytes and isolated larger lymphoid cells with prominent nucleoli, reminiscent of Hodgkin and Reed/Sternberg cells. In addition, an EBV-positive cell population with increased proliferation activity (Ki-67) was seen.

Considering the strong suspicion of immunosuppression-related EBV reactivation that had led to development of lymphoma, we decided a wait-and-see procedure. The abdominal and thoracic CT scans carried out one month later showed a significant reduction of the liver and mediastinal masses, fitting the clinical improvement of the patient (Figure 7-2). Furthermore, the re-testing for EBV DNA showed a titer below the detection limit of < 250 copies/mL.

The patient was discharged afterwards in significantly improved performance status, and a regular follow-up was started. Taking together our findings, we established the diagnosis of EBV-associated Hodgkin-like lymphoma caused by immunosuppressive therapy with azathioprine.

After three years, the patient has neither developed a recurrence of lymphoma nor showed symptoms of an active lupus erythematosus or autoimmune hepatitis. However, EBV copies in the range of 250 – 6,700 copies/mL are still detectable during follow-up, but the patient shows no clinical evidence of disease.

Figure 7-2 CT scan with significantly decreased liver lesion three months after discharge.



7.3. Discussion

It is a difficult task to make a definitive statement about the contribution of a specific immunosuppressant to the development of a specific malignancy like Hodgkin lymphoma. The incidence of these malignancies is very low; moreover, most autoimmune diseases are regarded as risk factors for the development of certain types of cancer, particularly lymphoma[210].

Among the immunosuppressive drugs, methotrexate plays a particular role, since the relationship between methotrexate treatment and the development of LPDs

is widely accepted. The withdrawal of methotrexate leads to regression in ~ 60% of the reported cases and even 100% in Hodgkin lymphoma- like lesions[211]. Therefore, “methotrexate-associated LPDs” were incorporated as a separate entity in the 2008 WHO classification of immunodeficiency-associated LPDs.

For azathioprine, however, the association is less well established despite there is very good evidence that the use of thiopurines (azathioprine and 6-mercaptopurine) increases the risk of lymphoma in some underlying diseases. For instance, two metaanalyses and a prospective cohort trial all show a 4- to 6-fold increase in the risk for LPDs for patients with inflammatory bowel disease treated with azathioprine[212–215]. However, for other autoimmune diseases like autoimmune hepatitis, the relationship between administration of azathioprine and the development of LPD, especially Hodgkin-like lymphoma, has not been established. This is due to the scarce data on the few published cases and the fact that azathioprine-related LPDs differ from methotrexate-related lymphomas. A study about therapy-related lymphomas after treatment with disease-modifying antirheumatic drugs revealed that methotrexate-associated cases respond well to withdrawal of the immunosuppressant, implying that immunosurveillance was important in lymphomagenesis, while azathioprine-related lymphomas tend to be EBV-negative and respond poorly to cessation of immunosuppressive therapy[216]. This is consistent with our literature search for azathioprine-induced, EBV-associated LPDs with focus on autoimmune hepatitis as underlying disease.

In the case of a woman with autoimmune hepatitis published by Sakai et al.[217], the patient developed marginal zone B cell lymphoma of the MALT type after immunosuppressive treatment with azathioprine and prednisolone. Since this patient achieved complete remission after chemotherapy with cyclophosphamide, pirarubicin (tetrahydropyranyl adriamycin), vincristine, and prednisolone, the relative contribution of azathioprine to the development of the lymphoma cannot be determined. The same applies to the other two cases[218,219] described in the literature who developed LPD (intravascular large B cell lymphoma and classical Hodgkin lymphoma) under immunosuppressive therapy with azathioprine for autoimmune hepatitis. Both of them achieved complete response after chemotherapy and cessation of azathioprine, and therefore, the association between immunosuppression by azathioprine and the

development of LPD is only speculative in this cases. Nevertheless, in both cases, the presence of EBV early region DNA (EBER) was assessed.

Most treatment recommendations for various kinds of EBV-associated LPD under immunosuppression have the scope to restore immune response to EBV-infected cells. This can be achieved by reduction or cessation of immunosuppressive agents if possible, which can lead to T cell reconstitution that eliminates or at least controls EBV-infected malignant cells. The strategy of tapering or stopping immunosuppression can be very successful but needs careful monitoring of the patient. Furthermore, it seems to be more promising in early lesions.

Another option for the treatment of EBV-associated LPD is the chimeric monoclonal anti-CD20 antibody rituximab. This approach is directed towards the destruction of EBV-infected $CD20^+$ B cells. It is a well-established agent for post-transplant lymphoproliferative disorder PTLD after hematopoietic stem cell transplantation HSCT. Response rates of ~ 55 – 100% have been published[220–223].

Cytotoxic chemotherapy is another therapeutic option for treating these malignancies. This mainly includes regimens that are widely used in standard lymphoma therapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) for non-Hodgkin lymphoma or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) for Hodgkin lymphoma. Nevertheless, there are many concerns regarding this treatment as it increases immunosuppression and deteriorates the immune response of the patient. This increases the risk of opportunistic infections and limits the response rate. However, one study in which the CHOP regimen was used for treating LPD reports a response rate of 65% and a median overall survival of 42 months[224].

In some situations, particularly in the case of lymphoma with CNS involvement, a multimodal treatment might be necessary. Henkenberens et al.[225] published a rare case of primary EBV-positive Hodgkin's lymphoma with isolated intracranial involvement, which was successfully treated with a regimen consisting of surgical resection, systemic chemotherapy, and local postoperative irradiation. However, another case of a primary EBV-positive CNS (diffuse large B cell) lymphoma from recent years was successfully treated with a complex chemotherapy regimen containing sequential therapy with rituximab, high-dose methotrexate, cytarabine,

cyclofosfamide, ifosfamide, vincristine, vinblastine, and dexamethasone combined with intrathecal cytarabine[226]. It is worth mentioning that both cases of primary CNS lymphoma developed under immunosuppressive therapy with azathioprine.

The successful treatment of our patient was due to many circumstances: a progressive leukopenia prompted us to stop azathioprine therapy a few days after admission. The diagnostic workup of the patient took more than two weeks, mainly due to reference pathology. In the meantime, prednisone given as a „pre-phase lymphoma therapy“ lead to an impressive clinical improvement, so there was no need to re-establish azathioprine therapy. Thus, it was possible to completely stop the suspected immunosuppressive drug, unlike in many cases of post-transplantation LPD after hematopoietic stem cell transplantation or solid organ transplantation.

7.4. Conclusion

In conclusion, while data for the contribution of the immunosuppressant methotrexate to the development of EBV-associated LPDs is fairly clear, the available data for azathioprine is less evident. The patient reported by us was immunosuppressed with azathioprine for autoimmune hepatitis. The development of an EBV-associated Hodgkin-like lymphoma under this immunosuppressive therapy, and especially the regression of the lymphoma after cessation of azathioprine, confirms the relationship between this immunosuppressant, EBV infection, and the development of Hodgkin-like lymphoma. Therefore, albeit in rare cases, azathioprine-related lymphomas may respond to mere cessation of immunosuppressive therapy without need for chemotherapy.

8. Severe drug-induced liver injury as adverse drug event of antibiotics - Case Report and review of the literature

Munz M, Grummich H, Birkmann J, Wilhelm M, Holzgrabe U, Sörgel F. Severe Drug-Induced Liver Injury as an Adverse Drug Event of Antibiotics: A Case Report and Review of the Literature. Chemotherapy. 2017;62(6):367-373.

8.1. Introduction

Acute liver failure (ALF) is a complex multisystemic illness that evolves after severe damage and loss of function of most liver cells accompanied by coagulopathy and encephalopathy within a short period of time[231]. Apart from viral infections, drug-induced liver injury (DILI) is one of the main reasons for ALF. DILI can either be caused by predictable type A (augmented pharmacological) reactions, e.g. to acetaminophen[232–234], or type B (idiosyncratic) reactions. Type B reactions are not dose dependent and occur rarely, and thus are not predictable, as it is the case with most antibiotics[235]. We report a case of a young patient in whom different antibiotics, the analgesic and antipyretic acetaminophen or a combination of these drugs may have led to DILI resulting in life-threatening ALF.

8.2. Case Report

A 20-year-old woman was admitted to our hospital because of hepatitis of unknown origin. The patient's history was complex: five weeks before admission to our department a right cervical and nuchal lymph node swelling with odynophagia and fever up to 38.5 °C had been observed. An outpatient treatment had been commenced with amoxicillin (without clavulanic acid) and aspirin. Since no improvement occurred after three days, the treatment was changed to ciprofloxacin. After two more days without signs of recovery, the patient was admitted to the department of otorhinolaryngology the following day, where she received intravenous cefazolin, leading to a rapid improvement of the symptoms and a CRP decrease from 6.7 to 2.9 mg/dL (normal <0.5 mg/dL). At that time there were no signs of liver injury.

However, during the treatment she complained of generalized pruritus and developed fine-spotted red lesions on her trunk. As this rash was supposed to be caused by amoxicillin, the antibiotic treatment was changed to clindamycin and an antiallergic treatment with prednisone and an antihistaminic drug (levocetirizine) was

initiated. The patient was discharged from the hospital after four days. Acetaminophen was prescribed with the recommendation to take it in case of fever. Two weeks later the patient developed persistent fever up to 40 °C, which was again treated with acetaminophen for approximately one week (2 g/day).

When the patient was admitted to our department three weeks after discharge from the department of otorhinolaryngology (and 20 days after the first intake of acetaminophen), she still had a slight exanthema, a cervical lymphadenopathy, and signs of hepatitis. Upon admission, her laboratory values of liver function were as follows: total bilirubin 3.7 mg/dL (normal <1.0), alkaline phosphatase 143 U/L (normal 35-105), γ-glutamyltransferase 201 U/L (normal <40), aspartate aminotransferase (AST) 1153 U/L (normal <35), alanine transaminase (ALT) 1219 U/L (normal <35), glutamate dehydrogenase 54.2 U/L (normal <5), cholinesterase 2.6 kU/L (normal 3.9-10.3), and lactate dehydrogenase (LDH) 923 U/L (normal <250). Moreover, coagulation was compromised (international normalized ratio 1.57). Due to the highly elevated aminotransferase levels and, in contrast, the only slightly increased alkaline phosphatase level, the liver damage was classified as hepatocellular.

During her eight days´ stay, intensive investigations and laboratory tests were performed to exclude a viral origin of her hepatitis. Serologic tests for hepatitis A, B, C, and E, cytomegalovirus, Epstein-Barr virus, enterovirus, HIV, and influenza B all depicted negative results. Tests for influenza A and parainfluenza were negative for IgM and positive for IgA and IgG. Thus, an acute or recent infection with influenza A or parainfluenza could not be excluded. There were no signs of autoimmune hepatitis; her copper excretion was within the normal range. It is noteworthy that the patient did not receive any further acetaminophen or anti-infective treatment at our department of oncology and hematology.

Since the patient’s general condition worsened continuously, a liver transplantation was considered. At this time, her liver values were as follows: total bilirubin 16.9 mg/dL, γ-glutamyltransferase 84 U/L, ALT 859 U/L, and LDH 606 U/L. The synthesis capacity of the liver, shown by blood coagulation, was considerably reduced: international normalized ratio 2.62, antithrombin 21% (normal, 80-120%), factor II 21%, factor V 57%, factor VII 20%, and factor IX 29%.

At the department of gastroenterology an endoscopic laparoscopy with liver biopsy was performed, revealing that 50% of the hepatocytes were necrotic. On the same day liver failure occurred, whereupon the patient was transferred to the intensive care unit (ICU). In view of all findings, a recovery of the liver was not expected and the patient was put on the transplant list. The patient remained stable at a low level with episodes of hepatic encephalopathy until at last, after two weeks in the ICU, her condition began to improve slowly. Finally, the liver function was sufficiently restored, making a transplant unnecessary. Three weeks after admission to the ICU, the patient could be transferred to the general ward and after another two weeks she was discharged from the hospital. Another three weeks later, her general condition had recovered very well and also her liver function tests had considerably improved: total bilirubin 2.2 mg/dL, alkaline phosphatase 127 U/L, γ-glutamyltransferase 156 U/L, AST 55 U/L, and ALT 52 U/L. On follow-up examination one month later the patient felt well, showing completely normalized liver synthesis function tests and transaminases.

8.3. Discussion and review of the literature

Establishing the diagnosis of DILI can be difficult due to the lack of specific symptoms or tests. To our knowledge, the most recent guideline for the diagnosis and management of DILI has been published by the American College of Gastroenterology (ACG)[236]. The guideline underlines that the diagnosis of DILI requires the cautious exclusion of other causes of liver disease, coupled with a careful review of the patient's medication history and an awareness of the hepatotoxicity profile of the administered drugs.

In order not to go beyond the scope of this report, only hepatotoxicity profiles of drugs which are relevant in this case will be discussed. Involved experts from various fields of internal medicine agreed on the following drugs as possible causative agents: amoxicillin, ciprofloxacin, cefazolin, clindamycin and acetaminophen.

To identify relevant articles relating to the hepatotoxic potential of these drugs, a literature search in the PubMed database was performed. The key words used were the international nonproprietary names (INN) of the drugs and "drug-induced liver injury" and "hepatotoxicity." Search filters were set to "English," "French," or "German" language and to "Humans" as the species. No time period was set. Thereafter, a

manual search was performed in which the references of the previously obtained papers were searched for relevant articles.

8.3.1. Hepatotoxicity of amoxicillin

Amoxicillin has little hepatotoxic potential when administered without clavulanic acid. A study conducted in Spain revealed an incidence for amoxicillin-associated DILI of 1 (99% CI 0.1-4.1) per 100000 person-years of exposure[237], and another study with data from the General Practitioners Research Database (GPRD) in the UK reported an incidence of 3 (95% CI 0.2-5) per 100000 prescriptions[238]. It is noteworthy that the combination with clavulanic acid raises the risk for DILI 6- to 27-fold versus amoxicillin alone[237–240]. The combination of amoxicillin and clavulanic acid also showed a significant association of different human leukocyte antigen (HLA) class II haplotypes and susceptibility of DILI[241–243]. However, to our knowledge there are no genetic polymorphisms discussed in the literature, which influence the risk or clinical course of DILI caused by amoxicillin without clavulanic acid.

A recent review lists the hepatic damage by amoxicillin without clavulanic acid as hepatocellular pattern[244], whereas there are a few case reports which describe cholestatic pattern of liver damage by amoxicillin[245,246]. One case report describes the development of a vanishing bile duct syndrome associated with amoxicillin therapy[247].

8.3.2. Hepatotoxicity of ciprofloxacin

The incidence of DILI caused by fluoroquinolones, particularly ciprofloxacin, seems to be in the same order of magnitude as the incidence of DILI by amoxicillin without clavulanic acid. A study in the US, which examined 300 cases of DILI, revealed that ciprofloxacin was implicated as causative agent in five out of 217 cases with ciprofloxacin being the only antibiotic prescribed. In comparison, amoxicillin without clavulanic acid was implicated in two cases, amoxicillin in combination with clavulanic acid in 23 cases[248].

A study on clinical course and liver injury pattern of twelve cases of DILI by fluoroquinolones showed that median time from starting the medication to either earliest sign of DILI or abnormal liver tests was only 2.5 days. “All patients were symptomatic, seven developed jaundice (defined as total serum bilirubin >2.5 mg/dL), eight were hospitalized for the DILI, three developed symptoms or signs of hepatic or

other organ failure, one ultimately required liver transplantation, and one died of liver failure. The patterns of enzyme elevations were evenly distributed among cholestatic (n = 4), hepatocellular (n = 4), and mixed (n = 4) categories"[249].

8.3.3. Hepatotoxicity of cefazolin

With the exception of ceftriaxone, which can precipitate as calcium salt in the biliary vesicle producing biliary sludge, cephalosporins have little hepatotoxic potency. According to the review by Andrade and Tulkens, cholestasis appeared in all documented cases of cephalosporin-associated hepatotoxicity with symptoms manifesting within a few days of treatment[235]. For cefazolin a pubmed search revealed only three cases where cefazolin-induced liver injury was suspected[250–252]. However, the actual association between cefazolin and liver injury is questionable in two of the cases[250,251] since other drugs with hepatotoxic potential were given. The third case[252] provides no information whether the patient received other medication than cefazolin. Thus, none of the three cases could unambiguously confirm cefazolin as the definitive cause of the liver injury.

A recent study[253] examined the effect of drug–drug interactions on liver safety reports of four drugs highly associated with hepatotoxicity (acetaminophen, isoniazid, valproic acid, and amoxicillin/clavulanic acid). The co-administration of second-generation cephalosporins was associated with increased liver event reporting frequency (of amoxicillin/clavulanic acid), while the co-administration of third-generation cephalosporins even decreased the frequency of liver events (of amoxicillin/clavulanic acid and of acetaminophen). However, the effect of first-generation cephalosporins as cefazolin was not reported.

8.3.4. Hepatotoxicity of clindamycin

Data for clindamycin-associated hepatotoxicity are scarce. The product monograph of the clindamycin-containing drug Dalacin C describes one study with 216 volunteers who took in 1 or 2 grams of clindamycin daily for four weeks. "Despite one patient who developed infectious hepatitis during the study, laboratory tests showed no significant aberrations considered drug related. Occasional patients developed elevated serum transaminases and serum alkaline phosphatase."[254] Our literature search revealed only two case reports in recent years with clindamycin-induced liver

injury. In both of them the patterns of liver damage were mixed[255,256]. In the case published by Senanayake[255] the symptoms vanished within a few days after clindamycin was discontinued, while in the case presented by Aygün et al.[256], it took eight weeks for liver function tests to return to normal. Two reports from the 1970s also describe liver toxicity induced by clindamycin[257,258].

8.3.5. Hepatotoxicity of acetaminophen

The antipyretic drug acetaminophen is a common cause of ALF. It differs from the drugs discussed so far in the way that its hepatotoxicity is dose related and thus a type A reaction. The pharmacological principle of hepatotoxicity of acetaminophen is the activation of the drug to a toxic metabolite that is preferentially conjugated with glutathione. After depletion of glutathione reserves, the toxic metabolite, N-acetyl-p-benzoquinone imine, binds to nucleophilic groups of macromolecules in the cell, finally resulting in cell death of hepatocytes. Therefore, glutathione and its precursors, e.g. cysteine, serve as detoxifying agents[259]. This circumstance may explain why patients with decreased glutathione stores, e.g. alcoholics and malnourished patients, may be at increased risk of developing DILI associated with acetaminophen[260].

Since the hepatotoxicity of acetaminophen is dose dependent due to the described underlying mechanism, acetaminophen is generally regarded as save when administered according to the prescribing information[233,261–263]. To assess whether a certain drug is the cause of liver injury, the CIOMS/RUCAM scale (see Figure 8-1) was introduced in the 1990s. It is recognized to be the best evaluation system currently in use to establish a causal relationship between a potentially liver toxic drug and liver damage[244,264]. It involves a scoring system which categorizes the suspicion into "definite or highly probable" (score > 8), "probable" (score 6-8), "possible" (score 3-5), "unlikely" (score 1-2) and "excluded" (score ≤ 0)[265,266].

The problem in applying the CIOMS/RUCAM scale in this case is the difficulty to determine the onset of liver injury. Since the patient had not shown any sign of liver injury during her stay in the department of otorhinolaryngology but showed highly elevated transaminases when she was admitted to our department, we concluded that the onset of liver injury occurred during this period, very likely several days before she was presented to us. Thus, we cannot exclude one of the administered drugs as unrelated due to the temporal relationship (according to CIOMS/RUCAM scale: ≤15

days from cessation of the drug). The CIOMS/RUCAM scores for the administered drugs are shown in Table 8-1. Thus, according to the CIOMS/RUCAM scale, all of the named drugs may be categorized as “probable” causes for the hepatotoxic reaction in the present case.

Despite acetaminophen being characterized by a CIOMS/RUCAM score of seven and thus being categorized as “probable” in this evaluation system, we consider it unlikely for acetaminophen as single agent to cause the described hepatotoxic reaction. We justify our rating for acetaminophen on the dose-dependent manner of its hepatotoxicity and the fact that the patient had no risk factors like alcohol abuse or underlying disease, which would make a liver damage by low dose acetaminophen (2g/d) more likely. Moreover, the late onset of symptoms together with the clinical course and the relatively slow deterioration of liver function make it unlikely that acetaminophen was the cause of the liver damage.

The probability of cefazolin being the cause liver toxicity is also rather small. This hypothesis is based on the very small number of reports of liver toxicity caused by cefazolin. In the case of our patient, the late onset of symptoms after the cessation of cefazolin treatment makes its role as a causative drug even more unlikely. As mentioned above, the symptoms of cephalosporin-induced liver injury are reported to occur within a few days of treatment[235].

Due to the frequent prescription of this drug, ciprofloxacin hepatotoxicity is well known and often described despite its relatively low incidence. As stated before, ciprofloxacin-induced liver toxicity is reported to occur only 2.5 days (median) after the beginning of the medication[249]. As with acetaminophen and cefazolin, the late onset

of symptoms reduces the probability of ciprofloxacin being the causative agent for DILI in this case.

Clindamycin was the last antibiotic given before the liver enzymes began to rise. Hence, of all the administered substances, clindamycin shows the best temporal correlation between treatment and liver injury. Due to the scarce data of clindamycin-induced liver injury in the literature, the clinical course could not be relied upon to confirm or reject clindamycin as the causative agent.

In the course of antibiotic treatment, amoxicillin (without clavulanic acid) was the first drug administered. Thus, the time interval between treatment and the onset of

symptoms was the longest here. As long intervals between amoxicillin administration and liver injury are frequently described in the literature, there is a certain likelihood of amoxicillin-induced hepatotoxicity in our patient. Another argument indicating amoxicillin as the causative agent is the morbilliform exanthema, which developed a few days after the discontinuation of amoxicillin, suggesting an allergic reaction to amoxicillin. However, whether the documented allergic skin reaction to amoxicillin is an indicator for liver reaction or injury cannot be determined.

As the combination with clavulanic acid raises the risk for DILI versus amoxicillin alone, and these combinations often have names such as “amoxy plus,” the possibility of an erroneously prescription of amoxicillin-clavulanate was checked and excluded.

In view of all the findings, none of the administered drugs could reliably be excluded and, conversely, none of the substances could be designated as the definite cause of the liver toxicity observed. However, we come to the conclusion that amoxicillin or clindamycin, possibly with the involvement of acetaminophen, are the most probable causes of the described hepatoxicity.

8.4. Conclusion

In the case report presented by us, the patient developed ALF consistent with antibiotic-induced liver injury. This impressively shows that even well-tolerated antibiotics like betalactams or lincosamides may have severe side effects in rare cases and thus should be cautiously used and only with a clear indication. When prescribing potentially hepatotoxic drugs, clinicians should have a low threshold for checking their patients´ liver function, particularly when the clinical condition deteriorates or indicates a problem with liver function.

Figure 8-1 CIOMS/RUCAM scale[266].

	Hepatocellular type		Cholestatic or Mixed type		Assessment
1. Time to onset	Reaction occurred before starting the drug or >15 days after stopping the drug (except for slowly metabolized drugs)		Reaction occurred before starting the drug or >30 days after stopping the drug (except for slowly metabolized drugs)		
- Incompatible					Unrelated
- Unknown	No information available to calculate time to onset				Insufficiently documented
	1st exposure	2nd exposure	1st exposure	2nd exposure	Score
- From drug intake	5 to 90 days	1 to 15 days	5 to 90 days	1 to 90 days	+2
	<5 or >90 days	>15 days	<5 or >90 days	>90 days	+1
- From drug withdrawal	≤15 days	≤15 days	≤30 days	≤30 days	+1
2. Course of the reaction after cessation of the drug	Difference between the peak of ALT und upper limit of normal values		Difference between the peak of AP (or TB) und upper limit of normal values		
	Decrease ≥50% within 8 days		Not applicable		+3
	Decrease ≥50% within 30 days		Decrease ≥50% within 180 days		+2
	Not applicable		Decrease <50% within 180 days		+1
	Lack of information or no improvement		Lack of information or no improvement		0
	Decrease <50% after the 30th day or recurrent increase		-		-2
3. Risk factors	Alcohol		Alcohol or pregnancy		+1
	Age ≥ 55 years		Age ≥ 55 years		+1
4. Concomitant drug(s)	None or no information or concomitant drug with incompatible time to onset				0
	Concomitant drug with compatible or suggestive time to onset				-1
	Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset				-2
	Concomitant drug with evidence for its role in this case (positive re-challenge or validated test)				-3
5. Exclusion of non-drug causes Group I (6 causes): Recent viral infection with hepatitis viruses (1. HAV; 2. HBV; 3; HCV); 4. biliary obstruction; 5. alcoholism; 6. acute recent hypotension history Group II Complications of underlying disease(s); clinical and/or biological context suggesting CMV, EBV or herpes virus infection	All causes (group I and group II) reasonably ruled out				+2
	The 6 causes of group I ruled out				+1
	5 or 4 causes of group 1 ruled out				0
	Less than 4 causes of group I ruled out				-2
	Non-drug cause highly probable				-3
6. Previous information on hepatotoxicity of the drug	Reaction labeled in the product's characteristics				+2
	Reaction published but unlabeled				+1
	Reaction unknown				0
7. Response to re-administration	Doubling of ALT with the drug alone		Doubling of AP (or TB) with the drug alone		+3
	Doubling of ALT with the drugs already given at the time of the first reaction		Doubling of AP (or TB) with the drugs already given at the time of the first reaction		+1
	Increase of ALT but less than N in the same conditions as for the first administration		Increase of AP (or TB) but less than N in the same conditions as for the first administration		-2
	Other situations		Other situations		0

Table 8-1 CIOMS/RUCAM scores of administered antibiotics and acetaminophen.

	Amoxicillin	Ciprofloxacin	Cefazolin	Clindamycin	Acetaminophen
1. Time to onset					
- from beginning of the drug	2	2	2	2	2
- from cessation of the drug	1	1	1	1	1
2. Course					
- after cessation of the drug	2	2	2	2	2
3. Risk factors					
- ethanol	0	0	0	0	0
- age of the patient < 55 years	0	0	0	0	0
4. Concomitant drugs					
- concomitant drug known as	-2	-2	-2	-2	-2
5. Search for non drug causes					
- all causes reasonably ruled	2	2	2	2	2
6. Previous information on					
- reaction labelled in the	2	2	2	2	2
7. Response to readministration					
- not done or not interpretable	0	0	0	0	0
Total	7	7	7	7	7

9. List of abbreviations

%T	percentage of time in a dosing interval
ACG	American College of Gastroenterology
ADME	absorption, distribution, metabolism, and excretion of a drug
ALF	acute liver failure
ALT	alanine transaminase
AP (or ALP)	alkaline phosphatase
APACHE II (score)	Acute Physiology and Chronic Health Evaluation II (score)
aPTT	activated Partial Thromboplastin Time
AST	aspartate transaminase
AUC	area under the concentration-time curve
AUC_{24h}	area under the concentration-time curve over a 24 h interval
$AUC_{0-\infty}$	area under the concentration-time curve from time of administration up to time infinity
AUC_{0-t}	area under the concentration-time curve from zero to the time of the last sample collected
$AUC_{t-\infty}$	area under the concentration-time curve from the last sample collected to infinity
BEACOPP	chemotherapy regimen including: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone
beta-hCG	beta subunit of human chorionic gonadotropin
BMI	body mass index
BP	bone penetration
BPR	bone penetration ratio
c	concentration
CAVH	continuous arteriovenous hemofiltration
CD15	clusters of differentiation molecule 15
CD30	clusters of differentiation molecule 30
CD8	clusters of differentiation molecule 8
CHOP	chemotherapy regimen including: cyclophosphamide, doxorubicin, vincristine and prednisone or prednisolone
CIL	cilastatin
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CLCR	creatinine clearance
CL_{GFR}	glomerular filtration clearance
$CL_{GFR}(t)$	time-dependence of glomerular filtration clearance
CL_{NR}	nonrenal clearance
$CL_{NR,C}$	nonrenal clearance of cilastatin
$CL_{NR,I}$	nonrenal clearance of imipenem
$CL_{NR,MER}$	nonrenal clearance of meropenem
CL_R	renal clearance
$CL_{R,MER}$	renal clearance of meropenem
$CL_{R,MER}(t)$	time-dependence of renal clearance of meropenem
CLsec	tubular secretion clearance
$CLsec_C$	tubular secretion clearance of cilastatin
$CLsec_I$	tubular secretion clearance of imipenem
CL_T	total body clearance

Cmax	peak plasma (or serum) level
Cmin	trough plasma (or serum) level
CMV	cytomegalovirus
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
ΔCRP_{INF}	increase of CRP due to infection
ΔPCT_{INF}	increase of PCT due to infection
$c_{av.}^{SS.}$	average concentration after repeated dosing in steady state
c_{max}^{SS}	peak level after repeated dosing in steady state
c_{min}^{SS}	trough level after repeated dosing in steady state
CT	computed tomography
CV	coefficient of variation
CVVH	continuous venovenous hemofiltration
CVVHDF	continuous venovenous hemodiafiltration
DHP	dehydropeptidase
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EBER (DNA)	Epstein-Barr virus early region (deoxyribonucleic acid)
EBV	Epstein-Barr virus
ELF	epithelial lining fluid
ESI	electrospray ionization
EUCAST	European Committee on Antimicrobial Susceptibility Testing
F_{Filt}	glomerular filtration fraction for creatinine
fT>MIC	the time the concentration of the unbound drug is above the minimum inhibitory concentration
fu	non-protein bound fraction of drug in plasma
fu_I	non-protein bound fraction of imipenem in plasma
fu_C	non-protein bound fraction of cilastatin in plasma
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
GLDH	glutamate dehydrogenase
GPRD	General Practitioners Research Database
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hOAT1	human organic anion transporter 1
hOAT3	human organic anion transporter 3
HPLC	high performance liquid chromatography
HSCT	hematopoietic stem cell transplantation
IC	initial condition
IC_{CRP}	concentration of C-reactive protein at baseline
IC_{PCT}	concentration of procalcitonin at baseline
ICU	intensive care unit
IL-2	interleukin-2
IMI	imipenem
INR	international normalized ratio
IQR	inter quartile range
ke	elimination rate constant

K_M	Michaelis-Menten constant
$K_M sec_C$ (no sepsis)	Michaelis-Menten constant for tubular secretion clearance of cilastatin in patients without sepsis
$K_M sec_C$ (sepsis)	Michaelis-Menten constant for tubular secretion clearance of cilastatin in patients with sepsis
LC	Liquid chromatography
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LDH	lactate dehydrogenase
logD	logarithm of the distribution coefficient
logP	logarithm of the partition coefficient
LPD	lymphoproliferative disorder
m/z	mass-to-charge ratio
MALT (lymphoma)	mucosa associated lymphoid tissue (lymphoma)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MER	meropenem
MIC	minimum inhibitory concentration
MRM	Multiple Reaction Monitoring
MS	mass spectrometry
NCA	non-compartmental analysis
PAX-5	paired box protein 5
PCT	procalcitonin
PD	pharmacodynamics
PK	pharmacokinetics
pka	acid dissociation constant
POP-PK	population pharmacokinetics
PTLD	post-transplant lymphoproliferative disorder
q12h	every 12 hours
q24h	every 24 hours
q6h	every 6 hours
q8h	every 8 hours
r	Pearson correlation coefficient
R	infusion rate
R^2	Coefficient of determination
RDW	red blood cell distribution width
RF1/2/3	fractional changes of renal function after the first (RF1) / second (RF2) / third change time (RF3)
$RF1/2/3_{NO}$	fractional change of renal function at time T1/2/3 in patients without sepsis
$RF1/2/3_{SEP}$	fractional change of renal function at time T1/2/3 in patients with sepsis
RSE	residual standard error
RUCAM	Roussel Uclaf Causality Assessment Method
SCr	serum creatinine level
SD	standard deviation
SLED	sustained low-efficiency dialysis
SOFA (score)	sepsis-related organ failure assessment (score)
SPC	summary of product characteristics
spp.	species
SSI	surgical site infections
T	dosing interval
$t_{1/2}$	half-life

T1/2/3	time of first/second/third change of renal function
$t1/2_{CRP}$	half-life of turnover of CRP
$t1/2_{PCT}$	half-life of turnover of PCT
$t1/2_{RF}$	half-life for the rate of change of renal function
T3	triiodothyronine
T4	thyroxine
TB	total bilirubin
TDM	therapeutic drug management/monitoring
T_{Infect}	modeled time of infection
t_{max}	time at which the Cmax is observed
$T_{Rise,Inf}$	delay time between modeled time of infection and rise of CRP and PCT
TSH	thyroid stimulating hormone
TTURN	half-life of change (of renal function)
UHPLC	ultra-high performance liquid chromatography
V_1	volume of distribution of the central compartment
V_{1C}	volume of distribution of the central compartment for cilastatin
V_{1I}	volume of distribution of the central compartment for imipenem
VAP	ventilator associated pneumonia
Vd	volume of distribution
Vss	steady state volume of distribution
Vz	terminal phase volume of distribution
Γ	exponent of relationship between clearance of meropenem and creatinine

10. Summary

In the „Position Paper of the Division of Clinical Pharmacy of the German Pharmaceutical Society (DPhG)" clinical pharmacy is defined as the science and practice of the rational use of drugs[1], which includes the individualization of drug therapy. Clinical pharmacists therefore need a profound knowledge of the pharmacokinetic properties of relevant drugs, and clinical factors that are influencing these properties.

Against the background of individualizing drug therapy, pharmacokinetic and clinical factors are studied in this thesis.

In order to obtain an overview of the existing data on the pharmacokinetics of imipenem / cilastatin and meropenem in critically ill patients, a literature review for each of these carbapenem antibiotics was performed. These reviews included studies in critically ill patients as well as studies in healthy volunteers. While the reported results of studies in healthy volunteers had a small variability, studies in critically ill patients show significant differences in the resulting pharmacokinetics. These differences were not only between, but also within these studies, resulting in a high variability of the pharmacokinetic parameters of the carbapenems in critically ill patients. Furthermore, the results of studies in critically ill patients indicate that clinical factors and in particular renal function have different effects on the pharmacokinetics of imipenem and cilastatin.

A therapeutic drug monitoring (TDM) program for antibiotics was initiated in an intensive care unit. The calculation of the pharmacokinetics of imipenem / cilastatin and meropenem was carried out with a population pharmacokinetic approach (POP-PK) and in addition with a non-compartmental approach (NCA).

The POP-PK analysis showed that the pharmacokinetics of imipenem and cilastatin could be described adequately with a 1-compartment model. The resulting mean total body clearance (CL) of imipenem and cilastatin was 11.6 L/h (4.24 to 27.5) and 6.14 L/h (0.520 to 26.6 L/h). The nonrenal clearance was estimated to be 5.30 L / h (24.9% CV) for imipenem and 0.138 L / h (33.3% CV) for cilastatin.

The results of the NCA were in good agreement with the results of the POP-PK approach, as the NCA resulted in an imipenem clearance of 15.5 ± 7.3 L / hr and cilastatin clearance of 10.1 ± 9.9 L / h. The individual clearances resulting from the

different pharmacokinetic approaches were in good correlation showing correlation coefficients (r) of 0.882 ($p < 0.001$) and 0.908 ($p < 0.001$) for imipenem and cilastatin.

In summary, this study identified and quantified significant differences between the individual clearance mechanisms of imipenem and cilastatin. This is particularly true for patients with impaired renal function and sepsis. As imipenem / cilastatin is only available in a fixed dose combination, those patients might be treated inadequately with this combination. The great variability in the pharmacokinetics of imipenem and cilastatin in septic patients underscores the importance of a TDM program of both substances.

For meropenem, a PK/PD model was developed that predicts the concentration gradients of meropenem, serum creatinine, C-reactive protein and procalcitonin simultaneously. A non-linear relationship between the clearance of creatinine and meropenem was identified and the resulting equation for the calculation of the total body clearance of meropenem (for a 70 kg patient) was: 0.480 L/h + 9.86 L/h. $(CLCR/6L/h)^{0.593}$, with 0.480 L/h representing the nonrenal clearance of meropenem.

The resulting mean meropenem clearance of the NCA was 11.9 ± 8.7 L/h. The individual clearances resulting from the different pharmacokinetic approaches were poorly correlated showing a correlation coefficient (r) of 0.502 ($p < 0.001$).

In summary, this study showed a non-linear relationship of meropenem clearance and creatinine clearance. The model shows that the renal function may change rapidly and to a significant extent in patients with sepsis and septic shock, which in turn, underscores that creatinine concentrations are not in steady state in these patients. Conversely, dose adjustment based on creatinine values might lead to inappropriate therapy. This underlines the importance of a TDM program for meropenem in critically ill patients.

The two most important considerations when choosing an antibiotic for the prophylaxis of postoperative bone infections are its activity against the whole spectrum of bacteria, which might be involved in bone infections, and its ability to penetrate bone tissue and thus to achieve concentrations above the minimum inhibitory concentration (MIC) of the corresponding pathogens.

In order to gain information on this data, a study was conducted which investigated the pharmacokinetics of ampicillin / sulbactam in plasma, cortical and

cancellous bone. Pharmacokinetic parameters in plasma were determined using NCA. The bone penetration represents the ratio of the concentration in the bone tissue to plasma concentration at the time of bone removal. The resulting half-life of ampicillin and sulbactam in plasma was 1.60 ± 0.37 h and 1.70 ± 0.42 h. The elimination of both substances was in a good correlation with creatinine clearance and resulted in correlation coefficients (r) of 0.729 (p = 0.003) for ampicillin and 0.699 (p = 0.005) for sulbactam. The mean clearance and the mean volume of distribution of ampicillin and sulbactam were 10.7 ± 3.9 and 10.3 ± 3.3 L/h, and 23.9 ± 7.9 and 24.3 ± 6.8 L. The mean concentrations of ampicillin in the cortical and cancellous bone were 6.60 ± 4.22 and 10.15 ± 7.40 µg/g, resulting in bone penetration ratios of 9.1 ± 5.7 and 16.2 ± 16.9 %. For sulbactam the corresponding concentrations were 3.91 ± 2.52 and 5.73 ± 4.20 µg/g, resulting in bone penetration ratios of 10.6 ± 6.3 and 17.5 ± 16.1 %.

In summary, this study shows that the bone penetration of both substances is on average rather unsatisfactory and has a high variability, which can lead to inadequate bone concentrations for the prophylaxis of bone infections. One factor that could be identified for the penetration of both substances into cancellous bone was the period between the application of the drug and the removal of the bone. Therefore, a time interval between the administration of the antibiotic and the incision should be considered.

Immunosuppression is a risk factor for the development of various malignancies, including hematologic diseases. While the relationship between the use of immunosuppressive therapy with methotrexate and the development of an Epstein-Barr virus (EBV) associated lymphoproliferative disease (LPD) has been well established, this connection is less evident for immunosuppressive therapy with azathioprine.

The patient presented by us was immunosuppressed with azathioprine for autoimmune hepatitis. The development of an EBV-associated Hodgkin-like lymphoma under this immunosuppressive therapy and especially the regression of the lymphoma after cessation of azathioprine confirms the relationship between this immunosuppressant, EBV-infection and the development of Hodgkin-like lymphoma. Therefore, albeit in rare cases, azathioprine-related lymphomas may respond to mere cessation of immunosuppressive therapy without need for chemotherapy.

Apart from viral infections, drugs are a major cause of acute liver failure. Due to the lack of specific symptoms or tests, it is difficult to diagnose a drug-induced liver injury. We report a case of a young patient in whom different antibiotics, the analgesic and antipyretic acetaminophen or a combination of these drugs may have led to DILI resulting in life-threatening ALF. Based on this case report, we describe a procedure to exclude non-drug related causes and discuss the hepatotoxic potential of the involved drugs in this case.

11. Zusammenfassung

Im Positionspapier der Fachgruppe für Klinische Pharmazie der Deutschen Pharmazeutischen Gesellschaft (DPhG) wird Klinische Pharmazie als Wissenschaft und Praxis vom rationalen Arzneimitteleinsatz definiert[1]. Dies schließt auch die Therapie- und Dosisindividualisierung ein. Grundlage hierzu sind profunde Kenntnisse insbesondere der pharmakokinetischen Eigenschaften eines Arzneimittels, sowie klinischer Faktoren, welche diese beeinflussen.

In dieser Dissertation werden pharmakokinetische und klinische Einflussfaktoren untersucht, welche als Entscheidungsgrundlage für eine Dosis- und Therapie- Individualisierung dienen können.

Um einen Überblick über bereits existierende Daten zur Pharmakokinetik der Carbapenem-Antibiotika Imipenem / Cilastatin und Meropenem bei kritisch kranken Patienten zu erhalten, wurde für beide Carbapeneme eine Literaturübersicht erstellt, welche sowohl Studien an kritisch kranken Patienten, als auch an gesunden Probanden einbezieht. Während die Studien an gesunden Probanden zu relativ ähnlichen Ergebnissen bei den pharmakokinetischen Parametern führten, ergaben die Studien an kritisch kranken Patienten zum Teil erhebliche Unterschiede in der resultierenden Pharmakokinetik. Diese Unterschiede zeigten sich nicht nur zwischen, sondern auch innerhalb der Studien, was in einer hohen Variabilität der pharmakokinetischen Parameter bei kritisch kranken Patienten resultierte. Des Weiteren deuten die Ergebnisse der Studien an Patienten mit eingeschränkter Nierenfunktion darauf hin, dass klinische Faktoren wie insbesondere die Nierenfunktion, einen unterschiedlichen Einfluss auf die Pharmakokinetik von Imipenem und Cilastatin haben, welche ausschließlich in fixer Kombination verabreicht werden.

Im Folgenden wurde die Pharmakokinetik von Imipenem und Cilastatin bei kritisch kranken Patienten untersucht, deren Imipenem / Cilastatin Blutspiegel im Rahmen eines Therapeutischen Drug Monitoring (TDM) Programms bestimmt wurden. Die Berechnung der Pharmakokinetik erfolgte hier sowohl mit einem populationspharmakokinetischen Ansatz (POP-PK), als auch mit einer nicht-kompartimentellen Analyse (NCA). Die POP-PK Analyse ergab, dass die Pharmakokinetik beider Substanzen mit einem 1-Kompartiment Modell hinreichend

beschrieben werden kann. Für die Gesamt-Clearance (CL) ergaben sich Werte von 11.6 L/h (4.24 – 27.5) für Imipenem und 6.14 L/h (0.520 – 26.6) für Cilastatin. Für die nicht-renale Clearance ergab sich ein Wert von 5.30 L/h (24.9% CV) für Imipenem und 0.138 L/h (33.3% CV) für Cilastatin. Die Ergebnisse der NCA waren in guter Übereinstimmung mit den Ergebnissen des POP-PK Ansatzes. Für die Clearance von Imipenem und Cilastatin ergaben sich hier 15.5 ± 7.3 L/h bzw. 10.1 ± 9.9 L/h. Aus der Korrelation der Clearances beider PK-Analyse-Methoden ergaben sich Korrelationskoeffizienten (r) von 0.882 ($p<0.001$) und 0.908 ($p<0.001$) für Imipenem bzw. Cilastatin.

In Zusammenfassung identifizierte diese Untersuchung deutliche Unterschiede der einzelnen Clearance-Mechanismen von Imipenem und Cilastatin und quantifizierte diese. Diese Unterschiede kommen bei Patienten zum Tragen, deren Nierenfunktion eingeschränkt ist, insbesondere wenn diese Patienten septisch sind.

Die große Variabilität der Pharmakokinetik von Imipenem und Cilastatin bei septischen Patienten unterstreicht die Bedeutung eines TDM-Programms beider Substanzen. Bei Patienten mit stark beeinträchtigter Nierenfunktion kann die Verwendung der fixen Kombination von Imipenem / Cilastatin aufgrund der unterschiedlichen Pharmakokinetik ungeeignet sein.

In einem gesonderten Ansatz wurde die Pharmakokinetik von Meropenem bei kritisch kranken Patienten untersucht, deren Meropenem Blutspiegel ebenfalls im Rahmen des genannten TDM-Programms bestimmt wurden. Wie bei Imipenem / Cilastatin erfolgte die pharmakokinetische Analyse hier ebenfalls zuerst mit einem POP-PK Ansatz, der dann mit einem NCA-Ansatz nachvollzogen wurde.

Für Meropenem wurde ein PK/PD-Modell entwickelt, welches gleichzeitig die Konzentrationsverläufe von Meropenem, Serumkreatinin, C-reaktivem Protein und Procalcitonin vorhersagt. Dadurch konnte ein nicht-linearer Zusammenhang zwischen der Clearance von Meropenem und Kreatinin identifiziert werden. Die Gesamt-Clearance von Meropenem (für einen 70 kg Patienten) lässt sich anhand des Modells abschätzen nach: $0.480\ L/h + 9.86\ L/h \cdot (CL_{CR}/6\ L/h)^{0.593}$, wobei 0.480 L/h die nicht-renale Clearance von Meropenem repräsentiert.

Der NCA-Ansatz ergab eine Meropenem Clearance von 11.9 ± 8.7 L/h, wobei die Korrelation zum POP-PK Ansatz mit einem Korrelationskoeffizienten (r) von 0.502 ($p<0.001$) wesentlich schwächer war, als bei Imipenem und Cilastatin.

In Zusammenfassung zeigte diese Untersuchung einen nicht-linearen Zusammenhang der Meropenem-Clearance und der Kreatinin-Clearance. Das entwickelte Modell zeigt, dass sich die Nierenfunktion bei Patienten mit Sepsis und septischem Schock rapide und in erheblichem Ausmaß verändern kann, was wiederum dazu führt, dass sich die Kreatinin-Konzentrationen bei diesen Patienten in keinem Steady-State-Zustand befinden. Im Umkehrschluss bedeutet dies, dass eine Dosisanpassung anhand der Kreatinin-Werte zu einer inadäquaten Therapie führen kann. Dies unterstreicht die Bedeutung eines TDM-Programms für Meropenem bei kritisch kranken Patienten.

Die zwei bedeutsamsten Überlegungen bei der Auswahl eines Antibiotikums zur Prophylaxe einer postoperativen Knocheninfektion sind dessen Aktivität gegen das in Frage kommende Erregerspektrum, sowie die Fähigkeit des Antibiotikums Gewebe und insbesondere Knochengewebe zu penetrieren und damit Konzentrationen zu erreichen, welche über der minimalen Hemm-Konzentration (MHK) entsprechender Erreger liegen. Um eine Entscheidungsgrundlage für diese Fragestellung zu liefern, wurde eine Untersuchung durchgeführt, bei der die Pharmakokinetik von Ampicillin / Sulbactam in Plasma, kortikalem und spongiösem Knochen untersucht wurde.

Die pharmakokinetischen Parameter im Plasma wurden dabei mittels einer nicht-kompartimentellen Analyse bestimmt. Die Knochenpenetration stellt das Verhältnis der Konzentration im Knochengewebe zur Konzentration im Plasma zum Zeitpunkt der Knochenentnahme dar. Im Plasma ergab sich eine Halbwertszeit von 1.60 ± 0.37 h für Ampicillin und 1.70 ± 0.42 h für Sulbactam. Die Elimination beider Substanzen war damit in einer guten Korrelation mit der Kreatinin-Clearance, was in Korrelationskoeffizienten (r) von 0.729 ($p=0.003$) für Ampicillin und 0.699 ($p=0.005$) für Sulbactam resultierte. Die mittlere Clearance und das mittlere Verteilungsvolumen von Ampicillin bzw. Sulbactam waren 10.7 ± 3.9 bzw. 10.3 ± 3.3 L/h, und 23.9 ± 7.9 bzw. 24.3 ± 6.8 L. Die mittleren Konzentrationen von Ampicillin im kortikalen und spongiösen Knochen waren 6.60 ± 4.22 und 10.15 ± 7.40 µg/g, was in einer Knochenpenetration von 9.1 ± 5.7 und 16.2 ± 16.9 % resultierte. Für Sulbactam betrugen die

entsprechenden Konzentrationen 3.91 ± 2.52 und 5.73 ± 4.20 µg/g, was in einer Knochenpenetration von 10.6 ± 6.3 und 17.5 ± 16.1 % resultierte.

In Zusammenfassung zeigt diese Untersuchung auf, dass die Knochenpenetration beider Substanzen im Mittel eher ungenügend ist und eine hohe Variabilität besitzt, wodurch es zu inadäquaten Knochenkonzentrationen kommen kann. Ein Faktor, der zumindest für die Penetration in den spongiösen Knochen identifiziert werden konnte, war die Zeitspanne zwischen der Applikation und der Entnahme des Knochens, was eine Administration des Antibiotikums in zeitlichem Abstand zur Inzision sinnvoll erscheinen lässt.

Immunsuppression ist ein Risikofaktor für die Entwicklung verschiedener maligner Erkrankungen inklusive hämatologischer Erkrankungen. Während der Zusammenhang zwischen einer immunsuppressiven Therapie mit Methotrexat und der Entwicklung einer Eppstein-Barr-Virus (EBV) assoziierten lymphoproliferativen Erkrankung (LPD) durch die Datenlage gut belegt ist, ist dieser Zusammenhang für eine immunsuppressive Therapie mit Azathioprin weniger evident. Anhand eines Fallberichtes wird die Entwicklung eines Hodgkin-Lymphoms unter Therapie einer Auto-Immunhepatitis mit Azathioprin beschrieben, welches durch alleiniges Absetzen der immunsuppressiven Therapie reversibel war.

Neben viralen Erkrankungen sind Arzneimittel eine der Hauptursachen für akutes Leberversagen. Aufgrund des Fehlens spezifischer Symptome oder Tests ist es jedoch schwierig, eine Arzneimittel-induzierte Lebertoxizität zu diagnostizieren. Anhand eines Fallberichtes, welcher die Entwicklung eines akuten Leberversagens unter Therapie mit verschiedenen Antibiotika und Paracetamol beschreibt, wird ein Vorgehen zum Ausschluss sonstiger Ursachen beschrieben, sowie das lebertoxische Potential der beteiligten Arzneistoffe diskutiert.

12. References

1. Bertsche T, Derendorf H, Hempel G, et al. Positionspapier Klinische Pharmazie der Fachgruppe Klinische Pharmazie der DPhG. 2013.
2. Lesko LJ, Schmidt S. Individualization of drug therapy: history, present state, and opportunities for the future. *Clin Pharmacol Ther*. 2012;92(4):458-466. doi:10.1038/clpt.2012.113.
3. Nelson R. “One Size Fits All” Drug Dosing Gives Suboptimal Results. *Medscape Medical News - Conference News*. April 2013.
4. Kolb G, Rehmann P, Karbe-Voigt N, Wöstmann B. Are old patients not fit for clinical trials, or do clinical trials not fit to old patients? A survey in 35 pharmaceutical companies. *Eur Geriatr Med*. 2015. doi:10.1016/j.eurger.2015.04.003.
5. Bren L. Does Sex Make a Difference? *FDA Consum*. 2005;39(4):10-15.
6. Wuerzner G, Bochud M, Giusti V, Burnier M. Measurement of glomerular filtration rate in obese patients: Pitfalls and potential consequences on drug therapy. *Obes Facts*. 2011;4(3):238-243. doi:10.1159/000329547.
7. Chang CY, Schiano TD. Review article: Drug hepatotoxicity. *Aliment Pharmacol Ther*. 2007;25(10):1135-1151. doi:10.1111/j.1365-2036.2007.03307.x.
8. Goldstein SL, Nolin TD. Lack of drug dosing guidelines for critically ill patients receiving continuous renal replacement therapy. *Clin Pharmacol Ther*. 2014;96(2):159-161. doi:10.1038/clpt.2014.102.
9. McLeod HL. Clinically relevant drug – drug interactions in oncology. *Br J Clin Pharmacol*. 1998;45:539-544.
10. de Jong FA, Sparreboom A, Verweij J, Mathijssen RHJ. Lifestyle habits as a contributor to anti-cancer treatment failure. *Eur J Cancer*. 2008;44(3):374-382. doi:10.1016/j.ejca.2007.12.012.
11. Ampicillin-ratiopharm® Prescribing Information. ratiopharm GmbH, Ulm, Germany. 2015.
12. Ampicillin/Sulbactam Kabi® Prescribing Information. Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany. 2016.
13. Claforan® Prescribing Information. Sanofi-Aventis Deutschland GmbH,

Frankfurt am Main, Germany. 2017.
14. Cefuroxim-ratiopharm® Prescribing Information. ratiopharm GmbH, Ulm, Germany. 2015.
15. Klacid® Prescribing Information. Mylan Healthcare GmbH, Hannover, Germany. 2018.
16. Sobelin® Prescribing Information. Pfizer Pharma PFE GmbH, Berlin, Germany. 2017.
17. Eusaprim® Prescribing Information. Aspen Pharma Trading Limited, Dublin, Irland. 2017.
18. Cubicin ® Prescribing Information. Merck Sharp & Dohme Ltd, Hoddesdon, UK. 2018.
19. Fluconazol Kabi® Prescribing Information. Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany. 2017.
20. Zyvoxid® Prescribing Information. Pfizer Pharma PFE GmbH, Berlin, Germany. 2016.
21. Metronidazol Kabi® Prescribing Information. Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany. 2016.
22. Avalox® Prescribing Information. Bayer Vital GmbH,Leverkusen,Germany. 2017.
23. Piperacillin/Tazobactam Kabi® Prescribing Information. Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany. 2017.
24. Roxithromycin-ratiopharm® Prescribing Information. ratiopharm GmbH, Ulm, Germany. 2014.
25. Sprycel® Prescribing Information. Bristol-Myers Squibb Pharma EEIG, Uxbridge, UK. 2017.
26. Afinitor® Prescribing Information. Novartis Europharm Limited, Camberley, UK. 2017.
27. Iressa® Prescribing Information. AstraZeneca AB, Södertälje, Sweden. 2017.
28. Gemzar® Prescribing Information. Lilly Deutschland GmbH, Bad Homburg, Germany. 2017.
29. Tyverb® Prescribing Information. Novartis Europharm Limited, Camberley, UK. 2017.

30. Revlimid® Prescribing Information. Celgene Europe Limited, Uxbridge, UK. 2017.
31. Tasigna® Prescribing Information. Novartis Europharm Limited, Camberley, UK. 2017.
32. Paclitaxel Kabi® Prescribing Information. Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany. 2016.
33. Votrient® Prescribing Information. Novartis Europharm Limited, Camberley, UK. 2017.
34. Nexavar® Prescribing Information. Bayer Vital GmbH, Leverkusen, Germany. 2017.
35. Sutent® Prescribing Information. Pfizer Pharma PFE GmbH, Berlin, Germany. 2018.
36. Benet LZ, Zia-Amirhosseini P. Basic principles of pharmacokinetics. *Toxicol Pathol*. 1995;23(2):115-123. doi:10.1177/019262339502300203.
37. Gobburu J V, Holford NH. Vz, the terminal phase volume: time for its terminal phase? *J Biopharm Stat*. 2001;11(4):373-375. doi:10.1080/10543400500406629.
38. Cammann K. *Instrumentelle Analytische Chemie*. 1st ed. Heidelberg, Germany: Springer Spektrum; 2001.
39. Mass Spectrometry Ionization Methods. *Emory Univ Atlanta, GA, USA*.
40. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42(8):1749-1755. doi:10.1097/CCM.0000000000000330.
41. Vincent J-L, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323-2329. doi:10.1001/jama.2009.1754.
42. Engelmann L, Bellmann R. Adäquate Antibiotikatherapie auf der Intensivstation. *Med Klin Intensivmed Notfmed*. 2014;109(3):154-155. doi:10.1007/s00063-013-0301-8.
43. Bodmann KF. Current guidelines for the treatment of severe pneumonia and sepsis. *Chemotherapy*. 2005;51(5):227-233. doi:10.1159/000087452.

44. Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams. *Crit Care*. 2011;15(5):R206. doi:10.1186/cc10441.
45. Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. *Clin Infect Dis*. 2008;47 Suppl 1(Suppl 1):S32-S40. doi:10.1086/590064.
46. Lodise TP, Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis*. 2007;44(October 2004):357-363. doi:10.1016/S0734-3299(08)70539-2.
47. McKinnon PS, Paladino J a., Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *Int J Antimicrob Agents*. 2008;31:345-351. doi:10.1016/j.ijantimicag.2007.12.009.
48. Roberts JA, Kruger P, Paterson DL, Lipman J. Antibiotic resistance--what's dosing got to do with it? *Crit Care Med*. 2008;36(8):2433-2440. doi:10.1097/CCM.0b013e318180fe62.
49. Huttner A, Harbarth S, Hope WW, Lipman J, Roberts JA. Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for? *J Antimicrob Chemother*. 2015;70(12):3178-3183. doi:10.1093/jac/dkv201.
50. O'Neil, M.J. (Ed.). Imipenem. In: *Merck Index: The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 14th Ed.*; 2006:833.
51. Djukic M, Munz M, Sörgel F, Holzgrabe U, Eiffert H, Nau R. Overton's rule helps to estimate the penetration of anti-infectives into patients' cerebrospinal fluid. *Antimicrob Agents Chemother*. 2012;56(2):979-988. doi:10.1128/AAC.00437-11.
52. Standiford HC, Drusano GL, Bustamante CI, et al. Imipenem coadministered with cilastatin compared with moxalactam: Integration of serum pharmacokinetics and microbiologic activity following single-dose administration to normal volunteers. *Antimicrob Agents Chemother*. 1986;29(3):412-417. doi:10.1128/AAC.29.3.412.

53. RxList. Primaxin i.v. (imipenem and cilastatin for Injection). 2014.
54. Katzung B, Trevor A. Carbapenems. In: *Basic and Clinical Pharmacology, 13th Edition.*; 2014:781.
55. Hoffman J, Trimble J, Brophy GM. Safety of imipenem/cilastatin in neurocritical care patients. *Neurocrit Care*. 2009;10:403-407. doi:10.1007/s12028-008-9170-z.
56. Edwards SJ, Emmas CE, Campbell HE. Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. *Curr Med Res Opin*. 2005;21(5)(5):785-794. doi:10.1185/030079905X46223.
57. Zhanel GG, Simor AE, Vercaigne L, Mandell L. Imipenem and meropenem: Comparison of in vitro activity, pharmacokinetics, clinical trials and adverse effects. *Can J Infect Dis*. 1998;9(4):215-228.
58. Mattoes HM, Kuti JL, Drusano GL, Nicolau DP. Optimizing antimicrobial pharmacodynamics: Dosage strategies for meropenem. *Clin Ther*. 2004;26:1187-1198. doi:10.1016/S0149-2918(04)80001-8.
59. Craig WA. Editorial commentary: Are blood concentrations enough for establishing pharmacokinetic/pharmacodynamic relationships? *Clin Infect Dis*. 2014;58(8):1084-1085. doi:10.1093/cid/ciu055.
60. The European Committee on Antimicrobial Susceptibility testing. Breakpoint tables for interpretation of MICs and zone diameters Version 6.0, valid from 2016-01-01.
61. Drusano GL, Standiford HC, Bustamante CI, et al. The plasma pharmacokinetics of high dose (1 g) imipenem coadministered with 1 g cilastatin in six normal volunteers. *Eur J Clin Microbiol*. 1984;3(5):468-470. doi:10.1007/BF02017377.
62. Belzberg H, Zhu J, Cornwell EE, et al. Imipenem levels are not predictable in the critically ill patient. *J Trauma*. 2004;56(1):111-117. doi:10.1097/01.TA.0000056164.26493.28.
63. Couffignal C, Pajot O, Laouénan C, et al. Population pharmacokinetics of imipenem in critically ill patients with suspected ventilator-associated pneumonia and evaluation of dosage regimens. *Br J Clin Pharmacol*. 2014;78:1022-1034. doi:10.1111/bcp.12435.

64. Tegeder I, Bremer F, Oelkers R, Schobel H, Schu J. Pharmacokinetics of Imipenem-Cilastatin in Critically Ill Patients Undergoing Continuous Venovenous Hemofiltration. 1997;41(12):2640-2645.
65. Hashimoto S, Honda M, Yamaguchi M, Sekimoto M, Tanaka Y. Pharmacokinetics of imipenem and cilastatin during continuous venovenous hemodialysis in patients who are critically ill. *ASAIO*. 1997;43:84-88.
66. Kihara M, Ikeda Y, Shibata K, et al. Pharmacokinetic profiles of intravenous imipenem/cilastatin during slow hemodialysis in critically ill patients. *Clin Nephrol*. 1994;42(3):193-197.
67. Keller E, Fecht H, Böhler J, Schollmeyer P. Single-dose kinetics of imipenem/cilastatin during continuous arteriovenous haemofiltration in intensive care patients. *Nephrol Dial Transplant*. 1989;4:640-645.
68. Lipš M, Šiller M, Strojil J, Urbánek K, Balík M, Suchánková H. Pharmacokinetics of imipenem in critically ill patients during empirical treatment of nosocomial pneumonia: A comparison of 0.5-h and 3-h infusions. *Int J Antimicrob Agents*. 2014;44:358-362. doi:10.1016/j.ijantimicag.2014.05.011.
69. McKindley DS, Boucher BA, Hess MM, Croce MA, Fabian TC. Pharmacokinetics of aztreonam and imipenem in critically ill patients with pneumonia. *Pharmacotherapy*. 16:924-931.
70. Afshartous D, Bauer SR, Connor MJ, et al. Pharmacokinetics and Pharmacodynamics of Imipenem and Meropenem in Critically Ill Patients Treated With Continuous Venovenous Hemodialysis. *Am J Kidney Dis*. 2014;63(1):170-171. doi:10.1053/j.ajkd.2013.08.015.
71. Novelli A, Adembri C, Livi P, Fallani S, Mazzei T, De Gaudio AR. Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. *Clin Pharmacokinet*. 2005;44(5):539-549.
72. Fish DN, Teitelbaum I, Abraham E. Pharmacokinetics and Pharmacodynamics of Imipenem during Continuous Renal Replacement Therapy in Critically Ill Patients. *Society*. 2005;49(6):2421-2428. doi:10.1128/AAC.49.6.2421.
73. Mueller B a, Scarim SK, Macias WL. Comparison of imipenem pharmacokinetics in patients with acute or chronic renal failure treated with continuous hemofiltration. *Am J Kidney Dis*. 1993;21(2):172-179.

74. Sakka SG, Glauner AK, Bulitta JB, et al. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin in critically ill patients in a randomized, controlled trial. *Antimicrob Agents Chemother*. 2007;51(9):3304-3310. doi:10.1128/AAC.01318-06.
75. Dahyot-Fizelier C, Lefeuvre S, Laksiri L, et al. Kinetics of imipenem distribution into the peritoneal fluid of patients with severe peritonitis studied by microdialysis. *Clin Pharmacokinet*. 2010;49(5):323-334. doi:10.2165/11319370-000000000-00000.
76. Tegeder I, Schmidtko A, Bräutigam L, Kirschbaum A, Geisslinger G, Lötsch J. Tissue distribution of imipenem in critically ill patients. *Clin Pharmacol Ther*. 2002;71:325-333. doi:10.1067/mcp.2002.122526.
77. The European Committee on Antimicrobial Susceptibility testing. Breakpoint tables for interpretation of MICs and zone diameters Version 5.0, valid from 2015-01-01.
78. Dahyot C, Marchand S, Bodin M, Debeane B, Mimoz O, Couet W. Application of basic pharmacokinetic concepts to analysis of microdialysis data: Illustration with imipenem muscle distribution. *Clin Pharmacokinet*. 2008;47(3):181-189. doi:10.2165/00003088-200847030-00004.
79. Lee LS, Kinzig-Schippers M, Nafziger AN, et al. Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. *Diagn Microbiol Infect Dis*. 2010;68(3):251-258. doi:10.1016/j.diagmicrobio.2010.06.012.
80. Jaruratanasirikul S, Raungsri N, Punyo J, Sriwiriyajan S. Pharmacokinetics of imipenem in healthy volunteers following administration by 2 h or 0.5 h infusion. *J Antimicrob Chemother*. 2005;56(October):1163-1165. doi:10.1093/jac/dki375.
81. Adamis G, Papaioannou MG, Giamarellos-Bourboulis EJ, Gargalianos P, Kosmidis J, Giamarellou H. Pharmacokinetic interactions of ceftazidime, imipenem and aztreonam with amikacin in healthy volunteers. *Int J Antimicrob Agents*. 2004;23:144-149. doi:10.1016/j.ijantimicag.2003.07.001.
82. Norrby SR, Alestig K, Bjornegard B, et al. Urinary recovery of N-formimidoyl thienamycin (MK0787) as affected by coadministration of N-formimidoyl thienamycin dehydropeptidase inhibitors. *Antimicrob Agents Chemother*.

1983;23(2):300-307. doi:10.1128/AAC.23.2.300.

83. Toon S, Hopkins KJ, Garstang FM, Aarons L, Rowland M. Pharmacokinetics of imipenem and cilastatin after their simultaneous administration to the elderly. *Br J Clin Pharmacol*. 1987;23:143-149.
84. Norrby SR, Rogers JD, Ferber F, et al. Disposition of radiolabeled imipenem and cilastatin in normal human volunteers. *Antimicrob Agents Chemother*. 1984;26(5):707-714. doi:10.1128/AAC.26.5.707.
85. Signs SA, Tan JS, Salstrom SJ, File TM. Pharmacokinetics of imipenem in serum and skin window fluid in healthy adults after intramuscular or intravenous administration. *Antimicrob Agents Chemother*. 1992;36(7):1400-1403. doi:10.1128/AAC.36.7.1400.
86. Nilsson-Ehle I, Hutchison M, Haworth SJ, Norrby SR. Pharmacokinetics of meropenem compared to imipenem-cilastatin in young, healthy males. *Eur J Clin Microbiol Infect Dis*. 1991;10:85-88.
87. Dreetz M, Hamacher J, Eller J, et al. Serum bactericidal activities and comparative pharmakokinetics of meropenem and imipenem-cilastatin. *Antimicrob Agents Chemother*. 1996;40(1):105-109. doi:x.
88. Paradis D, Vallee F, Allard S, et al. Comparative study of pharmacokinetics and serum bactericidal activities of cefpirome, ceftazidime, ceftriaxone, imipenem, and ciprofloxacin. *Antimicrob Agents Chemother*. 1992;36(10):2085-2092. doi:10.1128/AAC.36.10.2085.
89. Norrby SR, Björnegård B, Ferber F, Jones KH. Pharmacokinetics of imipenem in healthy volunteers. *J Antimicrob Chemother*. 1983;12 Suppl D:109-124.
90. Norrby SR, Alestig K, Ferber F, et al. Pharmacokinetics and tolerance of N-formimidoyl thienamycin (MK0787) in humans. *Antimicrob Agents Chemother*. 1983;23(2):293-299. doi:10.1128/AAC.23.2.293.
91. Vogel F, Bodmann KF. Empfehlungen zur kalkulierten parenteralen Initialtherapie bakterieller Erkrankungen bei Erwachsenen. *Arzneimitteltherapie*. 2004:271-281.
92. Rodloff AC, Goldstein EJC, Torres A. Two decades of imipenem therapy. *J Antimicrob Chemother*. 2006;58(5):916-929. doi:10.1093/jac/dkl354.
93. Primaxin® i.v. Prescribing Information. Merck Sharp & Dohme Corp., a

subsidiary of Merck & Co., Inc. Whitehouse Station, NJ, USA. 2014.

94. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial beta-lactam concentrations in select critically Ill patients: Association between augmented renal clearance and low trough drug concentrations. *Chest*. 2012;142:30-39. doi:10.1378/chest.11-1671.
95. Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic drug monitoring of antimicrobials. *Br J Clin Pharmacol*. 2012;73:27-36. doi:10.1111/j.1365-2125.2011.04080.x.
96. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
97. Bauer RJ, Guzy S, Ng C. A survey of population analysis methods and software for complex pharmacokinetic and pharmacodynamic models with examples. *AAPS J*. 2007;9(1):E60-E83. doi:10.1208/aapsj0901007.
98. Bulitta JB, Bingölbali A, Shin BS, Landersdorfer CB. Development of a new pre- and post-processing tool (SADAPT-TRAN) for nonlinear mixed-effects modeling in S-ADAPT. *AAPS J*. 2011;13(2):201-211. doi:10.1208/s12248-011-9257-x.
99. Bulitta JB, Landersdorfer CB. Performance and robustness of the Monte Carlo importance sampling algorithm using parallelized S-ADAPT for basic and complex mechanistic models. *AAPS J*. 2011;13(2):212-226. doi:10.1208/s12248-011-9258-9.
100. Bulitta JB, Okusanya OO, Forrest A, et al. Population pharmacokinetics of fusidic acid: Rationale for front-loaded dosing regimens due to autoinhibition of clearance. *Antimicrob Agents Chemother*. 2013;57(1):498-507. doi:10.1128/AAC.01354-12.
101. Dost F. *Grundlagen Der Pharmacokinetik*. 2nd. Stuttgart: Thieme; 1968.
102. Gugeler N, Klotz U. *Einführung in Die Pharmakokinetik*. 2nd ed. Eschborn: Govi-Verlag Pharmazeutischer Verlag GmbH; 2000.
103. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient - Concepts appraised by the example of antimicrobial agents. *Adv Drug Deliv Rev*. 2014;77:3-11. doi:10.1016/j.addr.2014.07.006.
104. McKenzie C. Antibiotic dosing in critical illness. *J Antimicrob Chemother*.

2011;66(SUPPL. 2):25-31. doi:10.1093/jac/dkq516.

105. Norrby SR, Norrby SR. Imipenem/cilastatin: rationale for a fixed combination. 2015;7(Suppl 3):S447-51.
106. Nau R, Lassek C, Kinzig-Schippers M, Thiel A, Prange HW, Sörgel F. Disposition and elimination of meropenem in cerebrospinal fluid of hydrocephalic patients with external ventriculostomy. *Antimicrob Agents Chemother*. 1998;42(8):2012-2016.
107. Meropenem. Prescribing information. Hospira Deutschland GmbH. Munich, Germany. 2011.
108. Merrem. Prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. 2013.
109. Roberts JA, Kirkpatrick CMJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: Intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. *J Antimicrob Chemother*. 2009;64(1):142-150. doi:10.1093/jac/dkp139.
110. Wang D. Experience with extended-infusion meropenem in the management of ventilator-associated pneumonia due to multidrug-resistant Acinetobacter baumannii. *Int J Antimicrob Agents*. 2009;33(3):290-291. doi:10.1016/j.ijantimicag.2008.09.012.
111. Dulhunty JM, Roberts JA, Davis JS, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: A multicenter double-blind, randomized controlled trial. *Clin Infect Dis*. 2013;56:236-244. doi:10.1093/cid/cis856.
112. Chytra I, Stepan M, Benes J, et al. Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial. *Crit Care*. 2012;16(3):R113. doi:10.1186/cc11405.
113. Carlier M, Carrette S, Roberts JA, et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? *Crit Care*. 2013;17(3):R84. doi:10.1186/cc12705.

114. De Waele JJ, Carrette S, Carlier M, et al. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: A randomised controlled trial. *Intensive Care Med*. 2014;40:380-387. doi:10.1007/s00134-013-3187-2.
115. Krueger WA, Schroeder TH, Hutchison M, et al. Pharmacokinetics of meropenem in critically ill patients with acute renal failure treated by continuous hemodiafiltration. *Antimicrob Agents Chemother*. 1998;42(9):2421-2424.
116. Lodise TP, Sorgel F, Melnick D, Mason B, Kinzig M, Drusano GL. Penetration of meropenem into epithelial lining fluid of patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother*. 2011;55(4):1606-1610. doi:10.1128/AAC.01330-10.
117. Conte JE, Golden J a., Kelley MG, Zurlinden E. Intrapulmonary pharmacokinetics and pharmacodynamics of meropenem. *Int J Antimicrob Agents*. 2005;26:449-456. doi:10.1016/j.ijantimicag.2005.08.015.
118. Tomaselli F, Maier A, Matzi V, Smolle-Jüttner FM, Dittrich P. Penetration of meropenem into pneumonic human lung tissue as measured by in vivo microdialysis. *Antimicrob Agents Chemother*. 2004;48(6):2228-2232. doi:10.1128/AAC.48.6.2228-2232.2004.
119. Condon RE, Walker AP, Hanna CB, Greenberg RN, Broom A, Pitkin D. Penetration of meropenem in plasma and abdominal tissues from patients undergoing intraabdominal surgery. *Clin Infect Dis*. 1997;24 Suppl 2(pH 6):S181-S183.
120. Karjagin J, Lefeuvre S, Oselin K, et al. Pharmacokinetics of meropenem determined by microdialysis in the peritoneal fluid of patients with severe peritonitis associated with septic shock. *Clin Pharmacol Ther*. 2008;83(3):452-459. doi:10.1038/sj.clpt.6100312.
121. Ikawa K, Morikawa N, Ikeda K, Ohge H, Sueda T. Development of breakpoints of carbapenems for intraabdominal infections based on pharmacokinetics and pharmacodynamics in peritoneal fluid. *J Infect Chemother*. 2008;14:330-332. doi:10.1007/s10156-008-0624-1.
122. Deshpande P, Chen J, Gofran A, Murea M, Golestaneh L. Meropenem removal in critically ill patients undergoing sustained low-efficiency dialysis (SLED). *Nephrol Dial Transplant*. 2010;25:2632-2636. doi:10.1093/ndt/gfq090.

123. Chimata M, Nagase M, Suzuki Y, Shimomura M, Kakuta S. Pharmacokinetics of meropenem in patients with various degrees of renal function, including patients with end-stage renal disease. *Antimicrob Agents Chemother*. 1993;37(2):229-233. doi:10.1128/AAC.37.2.229.
124. Leroy A, Fillastre JP, Etienne I, Humbert G. Pharmacokinetics of Meropenem (ICI 194 , 660) and Its Metabolite (ICI 213 , 689) in Healthy Subjects and in Patients with Renal Impairment. *Antimicrob Agents Chemother*. 1992;36(12):2794-2799. doi:10.1128/AAC.36.12.2794.Updated.
125. Leroy A, Fillastre JP, Etienne I, Borsa-Lebás F, Humbert G. Pharmacokinetics of meropenem in subjects with renal insufficiency. *Eur J Clin Pharmacol*. 1992;42(5):535-538.
126. Thyrum PT, Yeh C, Birmingham B, Lasseter K. Pharmacokinetics of meropenem in patients with liver disease. *Clin Infect Dis*. 1997;24 Suppl 2:S184-S190.
127. Tröger U, Drust A, Martens-Lobenhoffer J, Tanev I, Braun-Dullaeus RC, Bode-Böger SM. Decreased meropenem levels in Intensive Care Unit patients with augmented renal clearance: Benefit of therapeutic drug monitoring. *Int J Antimicrob Agents*. 2012;40:370-372. doi:10.1016/j.ijantimicag.2012.05.010.
128. Pea F, Viale P, Cojutti P, Furlanut M. Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: A pharmacokinetics/pharmacodynamics-based approach. *Antimicrob Agents Chemother*. 2012;56:6343-6348. doi:10.1128/AAC.01291-12.
129. Wong G, Brinkman A, Benefield RJ, et al. An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units. *J Antimicrob Chemother*. 2014;69(5):1416-1423. doi:10.1093/jac/dkt523.
130. Woksepp H, Hällgren A, Borgström S, et al. High target attainment for β-lactam antibiotics in intensive care unit patients when actual minimum inhibitory concentrations are applied. *Eur J Clin Microbiol Infect Dis*. 2017;36(3):553-563. doi:10.1007/s10096-016-2832-4.
131. Hites M, Taccone FS, Wolff F, et al. Case-control study of drug monitoring of β-lactams in obese critically ill patients. *Antimicrob Agents Chemother*.

2013;57:708-715. doi:10.1128/AAC.01083-12.

132. Taccone FS, Laterre P-F, Dugernier T, et al. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. *Crit Care*. 2010;14:R126. doi:10.1186/cc9091.
133. Jamal JA, Mat-Nor MB, Mohamad-Nor FS, et al. Pharmacokinetics of meropenem in critically ill patients receiving continuous venovenous haemofiltration: A randomised controlled trial of continuous infusion versus intermittent bolus administration. *Int J Antimicrob Agents*. 2015;45(1):41-45. doi:10.1016/j.ijantimicag.2014.09.009.
134. Tsai D, Stewart P, Goud R, et al. Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis. *Int J Antimicrob Agents*. 2016;48(5):542-546. doi:10.1016/j.ijantimicag.2016.08.015.
135. Zhao H-Y, Gu J, Lyu J, et al. Pharmacokinetic and Pharmacodynamic Efficacies of Continuous versus Intermittent Administration of Meropenem in Patients with Severe Sepsis and Septic Shock: A Prospective Randomized Pilot Study. *Chin Med J (Engl)*. 2017;130(10):1139. doi:10.4103/0366-6999.205859.
136. Jaruratanasirikul S, Thengyai S, Wongpoowarak W, et al. Population pharmacokinetics and Monte Carlo dosing simulations of meropenem during the early phase of severe sepsis and septic shock in critically ill patients in intensive care units. *Antimicrob Agents Chemother*. 2015;59(6):2995-3001. doi:10.1128/AAC.04166-14.
137. Binder L, Schwörer H, Hoppe S, et al. Pharmacokinetics of meropenem in critically ill patients with severe infections. *Ther Drug Monit*. 2013;35(1):63-70. doi:10.1097/FTD.0b013e31827d496c.
138. Jaruratanasirikul S, Limapichat T, Jullangkoon M, Aeinlang N, Ingviya N, Wongpoowarak W. Pharmacodynamics of meropenem in critically ill patients with febrile neutropenia and bacteraemia. *Int J Antimicrob Agents*. 2011;38(3):231-236. doi:10.1016/j.ijantimicag.2011.04.019.
139. Jaruratanasirikul S, Sriwiriyajan S, Punyo J. Comparison of the pharmacodynamics of meropenem in patients with ventilator-associated pneumonia following administration by 3-hour infusion or bolus injection.

Antimicrob Agents Chemother. 2005;49(4):1337-1339. doi:10.1128/AAC.49.4.1337-1339.2005.

140. Lheureux O, Trepo E, Hites M, et al. Serum β-lactam concentrations in critically ill patients with cirrhosis: a matched case–control study. *Liver Int*. 2016;36(7):1002-1010. doi:10.1111/liv.13039.
141. Adnan S, Li JX, Wallis SC, et al. Pharmacokinetics of meropenem and piperacillin in critically ill patients with indwelling surgical drains. *Int J Antimicrob Agents*. 2013;42(1):90-93. doi:10.1016/j.ijantimicag.2013.02.023.
142. Alobaid AS, Brinkmann A, Frey OR, et al. What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients? *J Antimicrob Chemother*. 2016;71(3):696-702. doi:10.1093/jac/dkv412.
143. Seyler L, Cotton F, Taccone FS, et al. Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. *Crit Care*. 2011;15(3):R137. doi:10.1186/cc10257.
144. Bilgrami I, Roberts JA, Wallis SC, et al. Meropenem dosing in critically ill patients with sepsis receiving high-volume continuous venovenous hemofiltration. *Antimicrob Agents Chemother*. 2010;54:2974-2978. doi:10.1128/AAC.01582-09.
145. Isla A, Maynar J, Sánchez-Izquierdo JA, et al. Meropenem and continuous renal replacement therapy: in vitro permeability of 2 continuous renal replacement therapy membranes and influence of patient renal function on the pharmacokinetics in critically ill patients. *J Clin Pharmacol*. 2005;45:1294-1304. doi:10.1177/0091270005280583.
146. Isla A, Rodriguez-Gascon A, Troconiz IF, et al. Population pharmacokinetics of meropenem in critically ill patients undergoing continuous renal replacement therapy. *Clin Pharmacokinet*. 2008;47(3):173-180. doi:4733 [pii]\r10.2165/00003088-200847030-00003 [doi].
147. Langgartner J, Vasold A, Glück T, Reng M, Kees F. Pharmacokinetics of meropenem during intermittent and continuous intravenous application in patients treated by continuous renal replacement therapy. *Intensive Care Med*. 2008;34:1091-1096. doi:10.1007/s00134-008-1034-7.
148. Krueger WA, Neeser G, Schuster H, et al. Correlation of meropenem plasma

levels with pharmacodynamic requirements in critically ill patients receiving continuous veno-venous hemofiltration. *Chemotherapy*. 2003;49:280-286. doi:10.1159/000074527.

149. Robatel C, Decosterd LA, Biollaz J, Eckert P, Schaller MD, Buclin T. Pharmacokinetics and dosage adaptation of meropenem during continuous venovenous hemodiafiltration in critically ill patients. *J Clin Pharmacol*. 2003;43:1329-1340. doi:10.1177/0091270003260286.
150. Kitzes-Cohen R, Farin D, Piva G, De Myttenaere-Bursztein SA. Pharmacokinetics and pharmacodynamics of meropenem in critically ill patients. *Int J Antimicrob Agents*. 2002;19(2):105-110.
151. Giles LJ, Jennings AC, Thomson AH, Creed G, Beale RJ, McLuckie A. Pharmacokinetics of meropenem in intensive care unit patients receiving continuous veno-venous hemofiltration or hemodiafiltration. *Crit Care Med*. 2000;28(3):632-637.
152. Ververs TF, van Dijk A, Vinks SA, et al. Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous venovenous hemofiltration. *Crit Care Med*. 2000;28(10):3412-3416.
153. Tegeder I, Neumann F, Bremer F, Brune K, Lötsch J, Geisslinger G. Pharmacokinetics of meropenem in critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration. *Clin Pharmacol Ther*. 1999;65:50-57. doi:10.1016/S0009-9236(99)70121-9.
154. Langan KM, Jacob J, Jian U, et al. Pharmacokinetics of short versus extended infusion meropenem dosing in critically ill patients: a pilot study. 2014;1(3):190-196.
155. Mattioli F, Fucile C, Del Bono V, et al. Population pharmacokinetics and probability of target attainment of meropenem in critically ill patients. *Eur J Clin Pharmacol*. 2016;72(7):839-848. doi:10.1007/s00228-016-2053-x.
156. Thalhammer F, Traunmüller F, El Menyawi I, et al. Continuous infusion versus intermittent administration of meropenem in critically ill patients. *J Antimicrob Chemother*. 1999;43:523-527.
157. Petersson J, Giske CG, Eliasson E. Standard dosing of piperacillin and meropenem fail to achieve adequate plasma concentrations in ICU patients.

Acta Anaesthesiol Scand. 2016;60(10):1425-1436. doi:10.1111/aas.12808.

158. Goncalves-Pereira J, Silva NE, Mateus A, Pinho C, Povoa P. Assessment of pharmacokinetic changes of meropenem during therapy in septic critically ill patients. *BMC Pharmacol Toxicol*. 2014;15:21. doi:10.1186/2050-6511-15-21.
159. de Stoppelaar F, Stolk L, van Tiel F, Beysens A, van der Geest S, de Leeuw P. Meropenem pharmacokinetics and pharmacodynamics in patients with ventilator-associated pneumonia. *J Antimicrob Chemother*. 2000;46:150-151.
160. Jaruratanasirikul S. Comparison of the pharmacodynamics of meropenem in healthy volunteers following administration by intermittent infusion or bolus injection. *J Antimicrob Chemother*. 2003;52(3):518-521. doi:10.1093/jac/dkg378.
161. Krueger WA, Bulitta J, Kinzig-Schippers M, et al. Evaluation by Monte Carlo simulation of the pharmacokinetics of two doses of meropenem administered intermittently or as a continuous infusion in healthy volunteers. *Antimicrob Agents Chemother*. 2005;49:1881-1889. doi:10.1128/AAC.49.5.1881-1889.2005.
162. Mouton JW, Michel MF. Pharmacokinetics of meropenem in serum and suction blister fluid during continuous and intermittent infusion. *J Antimicrob Chemother*. 1991;28:911-918.
163. Ljungberg B, Nilsson-Ehle I. Pharmacokinetics of Meropenem and Its Metabolite in Young and Elderly Healthy Men. *Antimicrob Agents Chemother*. 1992;36(7):1437-1440.
164. Dandekar PK, Maglio D, Sutherland CA, Nightingale CH, Nicolau DP. Pharmacokinetics of meropenem 0.5 and 2 g every 8 hours as a 3-hour infusion. *Pharmacotherapy*. 2003;23(8):988-991.
165. Wenzler E, Gotfried MH, Loutit JS, et al. Plasma, Epithelial Lining Fluid, and Alveolar Macrophage Concentrations of Meropenem-RPX7009 in Healthy Adult Subjects. *Antimicrob Agents Chemother*. 2015;59(September):AAC.01713-15. doi:10.1128/AAC.01713-15.
166. Kelly HC, Hutchison M, Haworth SJ. A comparison of the pharmacokinetics of meropenem after administration by intravenous injection over 5 min and intravenous infusion over 30 min. *J Antimicrob Chemother*. 1995;36 Suppl

A:35-41.
167. Burman LA, Nilsson-Ehle I, Hutchison M, Haworth SJ, Norrby SR. Pharmacokinetics of meropenem and its metabolite ICI 213,689 in healthy subjects with known renal metabolism of imipenem. *J Antimicrob Chemother*. 1991;27:219-224.
168. Leelarasamee A, Rongrungruang Y, Trakulsomboon S, Pongpech P, Thanawattanawanich P, Jithavech P. Bioequivalence, antibacterial activity and therapeutic outcome of a generic meropenem (Mapenem). *J Med Assoc Thai*. 2008;91(7):980-988.
169. Christensson BA, Nilsson-Ehle I, Hutchison M, Haworth SJ, Oqvist B, Norrby SR. Pharmacokinetics of meropenem in subjects with various degrees of renal impairment. *Antimicrob Agents Chemother*. 1992;36(7):1532-1537. doi:10.1128/AAC.36.7.1532.
170. Zavascki AP, Bulitta JB, Landersdorfer CB, Rev E, Infect A. Combination Therapy for Carbapenem-resistant Gram-negative Bacteria. 2013;11(12):1333-1353.
171. Sieger B, Berman SJ, Geckler RW, Farkas SA. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Meropenem Lower Respiratory Infection Group. *Crit Care Med*. 1997;25(10):1663-1670.
172. Norrby SR, Newell PA, Faulkner KL, Lesky W. Safety profile of meropenem: international clinical experience based on the first 3125 patients treated with meropenem. *J Antimicrob Chemother*. 1995;36 Suppl A:207-223.
173. Niederman MS. Hospital-acquired pneumonia, health care-associated pneumonia, ventilator-associated pneumonia, and ventilator-associated tracheobronchitis: definitions and challenges in trial design. *Clin Infect Dis*. 2010;51 Suppl 1(Suppl 1):S12-S17. doi:10.1086/653035.
174. Jelliffe R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. *Am J Nephrol*. 2002;22(4):320-324. doi:65221.
175. Chiou WL, Hsu FH. A new simple and rapid method to monitor the renal function based on pharmacokinetic consideration of endogeneous creatinine.

Res Commun Chem Pathol Pharmacol. 1975;10(2):315-330.

176. Shibayama T, Sugiyama D, Kamiyama E, Tokui T, Hirota T, Ikeda T. Characterization of CS-023 (RO4908463), a novel parenteral carbapenem antibiotic, and meropenem as substrates of human renal transporters. *Drug Metab Pharmacokinet*. 2007;22(1):41-47.
177. Landersdorfer CB, Bulitta JB, Kirkpatrick CMJ, et al. Population pharmacokinetics of piperacillin at two dose levels: Influence of nonlinear pharmacokinetics on the pharmacodynamic profile. *Antimicrob Agents Chemother*. 2012;56(11):5715-5723. doi:10.1128/AAC.00937-12.
178. Merollini KMD, Zheng H, Graves N. Most relevant strategies for preventing surgical site infection after total hip arthroplasty: Guideline recommendations and expert opinion. *Am J Infect Control*. 2013;41(3):221-226. doi:10.1016/j.ajic.2012.03.027.
179. Whitehouse JD, Friedman ND, Kirkland KB, Richardson WJ, Sexton DJ. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. *Infect Control Hosp Epidemiol*. 2002;23(4):183-189. doi:10.1086/502033.
180. Southwell-Keely J, Russo R. Antibiotic prophylaxis in hip fracture surgery: a metaanalysis. *Clin Orthop*. 2004;(419):179-184. doi:10.1097/01.blo.0000122663.98590.7b.
181. Meehan J, Jamali A a, Nguyen H. Prophylactic antibiotics in hip and knee arthroplasty. *J Bone Joint Surg Am*. 2009;91:2480-2490. doi:10.2106/JBJS.H.01219.
182. Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. *Surgery*. 1989;106(4):750-6-7.
183. Bratzler DW, Houck PM, Infection S. Antimicrobial prophylaxis for surgery : an advisory statement from the National Surgical Infection Prevention Project. 2005;189:395-404. doi:10.1016/j.amjsurg.2005.01.015.
184. Katzung B. TA. Extended-Spectrum Penicillins (Aminopenicillins, Carboxypenicillins, and Ureidopenicillins). In: *Basic and Clinical Pharmacology, 13th Edition.*; 2014:776.

185. Warnke JP, Wildfeuer A, Eibel G, Pfaff G, Klammer A. Pharmacokinetics of ampicillin/sulbactam in patients undergoing spinal microneurosurgical procedures. *Int J Clin Pharmacol Ther*. 1998;36(5):253-257.
186. Williams JD. Beta-lactamases and beta-lactamase inhibitors. *Int J Antimicrob Agents*. 1999;12 Suppl 1:S3-7-7.
187. Dajani A. Use of Ampicillin/Sulbactam and Sultamicillin in Pediatric Infections: A Re-Evaluation. *J Int Med Res*. 2001;29:257-269. doi:10.1177/147323000102900401.
188. Patterson JE, Farrel P, Zervos MJ. Time-kill kinetic studies of ampicillin/sulbactam for beta-lactamase-producing enterococci. *Diagn Microbiol Infect Dis*. 14(6):495-499.
189. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Heal Pharm*. 2013;70:195-283. doi:10.2146/ajhp120568.
190. Meyers BR, Wilkinson P, Mendelson MH, Walsh S, Bournazos C, Hirschman SZ. Pharmacokinetics of ampicillin-sulbactam in healthy elderly and young volunteers. *Antimicrob Agents Chemother*. 1991;35(10):2098-2101.
191. Dehne MG, Mühling J, Sablotzki a, Nopens H, Hempelmann G. Pharmacokinetics of antibiotic prophylaxis in major orthopedic surgery and blood-saving techniques. *Orthopedics*. 2001;24:665-669.
192. Wildfeuer A, Mallwitz J, Gotthardt H, et al. Pharmacokinetics of ampicillin, sulbactam and cefotiam in patients undergoing orthopedic surgery. *Infection*. 1997;25(4):258-262. doi:10.1007/BF01713160.
193. Heibel H, Scheer M, Reuther T, et al. Ampicillin and sulbactam concentrations in the irradiated mandible after oral squamous cell cancer. *Mund Kiefer Gesichtschir*. 2005;9:214-219. doi:10.1007/s10006-005-0615-7.
194. Wildfeuer A, Müller V, Springsklee M, Sonntag HG. Pharmacokinetics of ampicillin and sulbactam in patients undergoing heart surgery. *Antimicrob Agents Chemother*. 1991;35(9):1772-1776.
195. Landersdorfer CB, Bulitta JB, Kinzig M, Holzgrabe U, Sörgel F. Penetration of antibacterials into bone: pharmacokinetic, pharmacodynamic and bioanalytical considerations. *Clin Pharmacokinet*. 2009;48(2):89-124.

196. Rickinson A. Epstein-Barr virus. *Virus Res*. 2002;82(1-2):109-113.
197. Rezk SA, Weiss LM. Epstein-Barr virus-associated lymphoproliferative disorders. *Hum Pathol*. 2007;38(9):1293-1304. doi:10.1016/j.humpath.2007.05.020.
198. Amon W, Farrell PJ. Reactivation of Epstein-Barr virus from latency. *Rev Med Virol*. 2005;15(3):149-156. doi:10.1002/rmv.456.
199. Dojcinov SD, Venkataraman G, Raffeld M, Pittaluga S, Jaffe ES. EBV positive mucocutaneous ulcer--a study of 26 cases associated with various sources of immunosuppression. *Am J Surg Pathol*. 2010;34(3):405-417. doi:10.1097/PAS.0b013e3181cf8622.
200. Pender MP. CD8+ t-cell deficiency, epstein-barr virus infection, vitamin d deficiency, and steps to autoimmunity: A unifying hypothesis. *Autoimmune Dis*. 2012;1(1). doi:10.1155/2012/189096.
201. Hislop AD, Taylor GS, Sauce D, Rickinson AB. Cellular responses to viral infection in humans: lessons from Epstein-Barr virus. *Annu Rev Immunol*. 2007;25:587-617. doi:10.1146/annurev.immunol.25.022106.141553.
202. Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. *N Engl J Med*. 2004;350(13):1328-1337. doi:10.1056/NEJMra032015.
203. Krensky AM, Bennett WM, Vincenti F. Immunosuppressants, Tolerogens, and Immunostimulants. In: Brunton L, ed. *Goodman & Gilman´s The Pharmacological Basis of Therapeutics.* 12th ed. New York: McGraw-Hill; 2011:1013-1014.
204. McKendry R. Purine analogues. In: Dixon J FB, ed. *Second Line Agents in the Treatment of Rheumatic Diseases*. New York: Marcel Decker; 1991:223–237.
205. Trotter JL, Rodey GE, Gebel HM. Azathioprine decreases suppressor T cells in patients with multiple sclerosis. *N Engl J Med*. 1982;306(6):365-366. doi:10.1056/NEJM198202113060614.
206. Bacon PA, Salmon M. Modes of action of second-line agents. *Scand J Rheumatol Suppl*. 1987;64:17-24.
207. Belmont H. Pharmacology and side effects of azathioprine when used in rheumatic diseases. In: Furst DE, ed. *UpToDate*. Waltham, MA. Accessed April

24, 2015.

208. Evans SJ, Watson DK, O´Sullivan M. Reversible Hodgkin's lymphoma associated with Epstein-Barr virus occurring during azathioprine therapy for SLE. *Rheumatology*. 2008;47(7):1103-1104. doi:10.1093/rheumatology/ken188.
209. Kamel OW, van de Rijn M, Weiss LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med*. 1993;328(18):1317-1321. doi:10.1056/NEJM199305063281806.
210. Smedby KE, Baecklund E, Askling J. Malignant lymphomas in autoimmunity and inflammation: A review of risks, risk factors, and lymphoma characteristics. *Cancer Epidemiol Biomarkers Prev*. 2006;15(11):2069-2077. doi:10.1158/1055-9965.EPI-06-0300.
211. Gaulard P, Swerdlow S, Harris N, Jaffe E, Sundstrom C. Other iatrogenic immunodeficiency-associated lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. International Agency for Research on Cancer; 2008:350–351.
212. Subramaniam K, D'Rozario J, Pavli P. Lymphoma and other lymphoproliferative disorders in inflammatory bowel disease: a review. *J Gastroenterol Hepatol*. 2013;28(1):24-30. doi:10.1111/jgh.12015.
213. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. 2009;374(9701):1617-1625. doi:10.1016/S0140-6736(09)61302-7.
214. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut*. 2005;54(8):1121-1125. doi:10.1136/gut.2004.049460.
215. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin*

Gastroenterol Hepatol. 2009;7(8):874-881. doi:10.1016/j.cgh.2009.01.004.

216. Au W-Y, Ma ESK, Choy C, et al. Therapy-related lymphomas in patients with autoimmune diseases after treatment with disease-modifying anti-rheumatic drugs. *Am J Hematol*. 2006;81(1):5-11. doi:10.1002/ajh.20508.
217. Sakai A, Katayama Y, Mizuno A, et al. MALT lymphoma producing IgG-kappa type M-protein. (Abstract). *Rinsho Ketsueki*. 2000;41(8):658-663.
218. Tranchida P, Bayerl M, Voelpel MJ, Palutke M. Testicular ischemia due to intravascular large B-cell lymphoma: a novel presentation in an immunosuppressed individual. *Int J Surg Pathol*. 2003;11(4):319-324.
219. Loo EY, Medeiros LJ, Aladily TN, et al. Classical Hodgkin lymphoma arising in the setting of iatrogenic immunodeficiency: a clinicopathologic study of 10 cases. *Am J Surg Pathol*. 2013;37(8):1290-1297. doi:10.1097/PAS.0b013e31828e6564.
220. Kuehnle I, Huls MH, Liu Z, et al. CD20 monoclonal antibody (rituximab) for therapy of Epstein-Barr virus lymphoma after hemopoietic stem-cell transplantation. *Blood*. 2000;95(4):1502-1505.
221. van Esser JWJ, Niesters HGM, Holt B Van Der, et al. Prevention of Epstein-Barr virus – lymphoproliferative disease by molecular monitoring and preemptive rituximab in high-risk patients after allogeneic stem cell transplantation. 2002;99(12):4364-4369.
222. Brunstein CG, Weisdorf DJ, DeFor T, et al. Marked increased risk of Epstein-Barr virus-related complications with the addition of antithymocyte globulin to a nonmyeloablative conditioning prior to unrelated umbilical cord blood transplantation. *Blood*. 2006;108(8):2874-2880. doi:10.1182/blood-2006-03-011791.
223. Powell JL, Bunin NJ, Callahan C, Aplenc R, Griffin G, Grupp SA. An unexpectedly high incidence of Epstein-Barr virus lymphoproliferative disease after CD34+ selected autologous peripheral blood stem cell transplant in neuroblastoma. *Bone Marrow Transplant*. 2004;33(6):651-657. doi:10.1038/sj.bmt.1704402.
224. Choquet S, Trappe R, Leblond V. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders following solid organ transplantation.

Haematologica. 2007;92(2):273-274.

225. Henkenberens C, Franzke A, Raab P, Oschlies I, Klapper W, Christiansen H. Primary EBV-positive Hodgkin's lymphoma of the CNS under azathioprine treatment: case report and review of the literature. *Strahlenther Onkol*. 2014;190(9):847-852. doi:10.1007/s00066-014-0670-9.
226. Glesner MK, Ocias LF, Larsen TS, Pedersen C. Primary CNS lymphoma in a patient treated with azathioprine. *BMJ Case Rep Publ online*. 2014. doi:10.1136/ bcr-2014-205108.
227. Brunton L. Goodman & Gilman´s The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill, 2011.
228. McKendry R. Purine analogues. In: Second Line Agents in the Treatment of Rheumatic Diseases. Dixon J, Furst BE (Eds, Marcel Decker, New York 1991).
229. Kamel OW, van de Rijn M, Weiss LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med*. 1993;328(18):1317-1321. doi:10.1056/NEJM199305063281806.
230. Swerdlow S, Campo E, Harris N. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissue. Lyon: IARC; 2008.
231. O'Grady JG. Acute liver failure. *Postgrad Med J*. 2005;81(953):148-154. doi:10.1136/pgmj.2004.026005.
232. James L. Acetaminophen-induced hepatotoxicity. 2003;31(12):1499-1506.
233. Tujios S, Fontana RJ. Mechanisms of drug-induced liver injury: from bedside to bench. *Nat Rev Gastroenterol Hepatol*. 2011;8(4):202-211. doi:10.1038/nrgastro.2011.22.
234. Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med*. 2006;354(7):731-739. doi:10.1056/NEJMra052270.
235. Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. *J Antimicrob Chemother*. 2011;66(7):1431-1446. doi:10.1093/jac/dkr159.
236. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2014;109(7):950-966. doi:10.1038/ajg.2014.131.

237. Sabaté M, Ibáñez L, Pérez E, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. *Aliment Pharmacol Ther*. 2007;25(12):1401-1409. doi:10.1111/j.1365-2036.2007.03338.x.
238. García Rodríguez LA, Stricker BH, Zimmerman HJ. Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. *Arch Intern Med*. 1996;156(12):1327-1332.
239. Salvo F, Polimeni G, Moretti U, et al. Adverse drug reactions related to amoxicillin alone and in association with clavulanic acid: data from spontaneous reporting in Italy. *J Antimicrob Chemother*. 2007;60(1):121-126. doi:10.1093/jac/dkm111.
240. de Abajo FJ, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Br J Clin Pharmacol*. 2004;58(1):71-80. doi:10.1111/j.1365-2125.2004.02133.x.
241. O'Donohue J, Oien KA, Donaldson P, et al. Co-amoxiclav jaundice: clinical and histological features and HLA class II association. *Gut*. 2000;47(5):717-720. doi:10.1136/gut.47.5.717.
242. Lucena MI, Molokhia M, Shen Y, et al. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. *Gastroenterology*. 2011;141(1):338-347. doi:10.1053/j.gastro.2011.04.001.
243. Donaldson PT, Daly AK, Henderson J, et al. Human leucocyte antigen class II genotype in susceptibility and resistance to co-amoxiclav-induced liver injury. *J Hepatol*. 2010;53(6):1049-1053. doi:10.1016/j.jhep.2010.05.033.
244. Robles M, Toscano E, Cotta J, Lucena MI, Andrade RJ. Antibiotic-induced liver toxicity: mechanisms, clinical features and causality assessment. *Curr Drug Saf*. 2010;5(3):212-222. doi:10.2174/157488610791698307.
245. Chaabane N Ben, Safer L, Njim L, Zakhama A, Saffar H. Cholestatic hepatitis related to amoxicillin. *Drug Chem Toxicol*. 2011;34(4):357-358. doi:10.3109/01480545.2010.545067.
246. Bolzan H, Spatola J, Castelletto R, Curciarello J. Intrahepatic cholestasis induced by amoxicillin alone. *Gastroenterol Hepatol*. 2000;23(5):237-239.
247. Schwarze C, Schmitz V, Fischer HP, Sauerbruch T, Spengler U. Vanishing bile

duct syndrome associated with elevated pancreatic enzymes after short-term administration of amoxicillin. *Eur J Gastroenterol Hepatol*. 2002;14(11):1275-1277. doi:10.1097/00042737-200211000-00019.

248. Chalasani N, Fontana RJ, Bonkovsky HL, et al. Causes, Clinical Features, and Outcomes From a Prospective Study of Drug-Induced Liver Injury in the United States. *Gastroenterology*. 2008;135(6):1924-1934.e4. doi:10.1053/j.gastro.2008.09.011.
249. Orman ES, Conjeevaram HS, Vuppalanchi R, et al. Clinical and histopathologic features of fluoroquinolone-induced liver injury. *Clin Gastroenterol Hepatol*. 2011;9(6):517-523.e3. doi:10.1016/j.cgh.2011.02.019.
250. Benyounes M, Horsmans Y, Galand C, Lambert M. Acute cytolytic hepatitis caused by cefazolin and metronidazole. *Gastroentérologie Clin Biol*. 19(8-9):740-741.
251. Ammann R, Neftel K, Hardmeier T, Reinhardt M. Cephalosporin-induced cholestatic jaundice. *Lancet*. 1982;2(8293):336-337.
252. Tange T. Histopathological identification of hepatic intramitochondrial crystalloid inclusions (IMCI). (Abstract). *Acta Pathol Jpn*. 1981;31(5):747-754.
253. Suzuki A, Yuen NA, Ilic K, et al. Comedications alter drug-induced liver injury reporting frequency: Data mining in the WHO VigiBase™. *Regul Toxicol Pharmacol*. 2015;72(3):481-490. doi:10.1016/j.yrtph.2015.05.004.
254. Pfizer. 2011. Product monograph Dalacin. Pfizer, Kirkland, Quebec, Canada.
255. Senanayake S. Possible acute hepatotoxicity from oral clindamycin. *Aust Prescr*. 2009;32:140.
256. Aygün C, Kocaman O, Gürbüz Y, Şentürk Ö, Hülagü S. Clindamycin-induced acute cholestatic hepatitis. *World J Gastroenterol*. 2007;13:5408-5410.
257. Hinthorn DR, Baker LH, Romig DA, Voth DW, Liu C. Endocarditis treated with clindamycin: relapse and liver dysfunction. *South Med J*. 1977;70:823-826.
258. Elmore M, Rissing JP, Rink L, Brooks GF. Clindamycin-associated hepatotoxicity. *Am J Med*. 1974;57(4):627-630.
259. Mitchell JR, Jollow DJ, Potter WZ, Gillette JR, Brodie BB. Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione. *J Pharmacol Exp Ther*. 1973;187(1):211-217.

260. Lauterburg BH, Velez ME. Glutathione deficiency in alcoholics: risk factor for paracetamol hepatotoxicity. *Gut*. 1988;29(9):1153-1157. doi:10.1136/gut.29.9.1153.
261. Larson AM. Acetaminophen Hepatotoxicity. *Clin Liver Dis*. 2007;11(3):525-548. doi:10.1016/j.cld.2007.06.006.
262. Chun LJ, Tong MJ, Busuttil RW, Hiatt JR. Acetaminophen hepatotoxicity and acute liver failure. *J Clin Gastroenterol*. 2009;43(4):342-349. doi:10.1097/MCG.0b013e31818a3854.
263. FDA Joint Meeting of the Drug Safety and Risk Management Advisory Committee. Liver Injury Related to the Use of Acetaminophen. June 29-30, 2009.
264. Andrade RJ, Robles M, Fernández-Castañer A, López-Ortega S, López-Vega MC, Lucena MI. Assessment of drug-induced hepatotoxicity in clinical practice: A challenge for gastroenterologists. *World J Gastroenterol*. 2007;13(3):329-340.
265. Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol*. 1990;11(2):272-276.
266. Danan G, Benichou C. Causality assessment of adverse reactions to drugs - I: A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries. *J Clin Epidemiol*. 1993;46(11):1323-1330. doi:10.1016/0895-4356(93)90101-6.
267. Anderson BJ, Holford NHG. Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics. *Annu Rev Pharmacol Toxicol*. 2008;48(1):303-332. doi:10.1146/annurev.pharmtox.48.113006.094708.
268. Bulitta JB, Duffull SB, Landersdorfer CB, et al. Comparison of the pharmacokinetics and pharmacodynamic profile of carumonam in cystic fibrosis patients and healthy volunteers. *Diagn Microbiol Infect Dis*. 2009;65:130-141.

13. Appendix

13.1. Supplementary information on chapter 5 - Individualizing meropenem prolonged infusions in intensive care unit patients via population modeling of renal function and infection biomarkers over time

13.1.1. Population pharmacokinetic modeling

13.1.1.1. Modeling of serum creatinine concentrations

Creatinine was modeled as an endogenous compound using a one-compartment model (see chapter 5, Figure 5-1). We used the Cockcroft & Gault equation[96] to predict creatinine production rate based on sex, age and body weight. Both meropenem and creatinine PK was scaled via an allometric body size model[267,268]. The expected creatinine clearance at baseline was calculated using the creatinine concentration at 0 h. We did not assume that creatinine concentrations were at steady state at 0 h and therefore allowed for a random deviation of the individual creatinine clearance from the creatinine clearance at 0 h predicted by the Cockcroft & Gault equation. This random deviation was achieved by multiplying with a factor (F_{Filt}) whose mean was estimated to be close to 1.

Renal function (i.e. $CL_{GFR}(t)$) could change up to twice during the study. The time points of change (*i.e.* T1 and T1 + T2) as well as the half-life of change of renal function ($t1/2_{RF}$) were estimated for each patient. The factors RF1 and RF2 described that extent of change in renal function at times T1 and T2 relative to $CL_{GFR}(t=0)$ at baseline (*i.e.* time zero). These factors were estimated with separate means and variability for patients with and without sepsis.

13.1.1.2. Modeling of meropenem plasma concentrations

The pharmacokinetics of meropenem was described by a one-compartment model with a time-delimited zero-order infusion [rate: R(1)] to represent the 3 h meropenem infusion:

$$\frac{dX_1}{dt} = R(1) - \left[CL_{R,MER}(t) + CL_{NR,MER}\right] \cdot C_1 \qquad \textit{Initial condition (IC): 0} \qquad \textit{Equation 15}$$

While the nonrenal clearance of meropenem ($CLnr_{,MER}$) was time-independent, renal clearance of meropenem ($CL_{R,MER}(t)$) was time dependent. The latter was

calculated as a function of creatinine clearance ($CL_{GFR}(t)$) normalized to a standard creatinine clearance of 6.0 L/h (equivalent to 100 mL/min).

$$CL_{R,MER}(t) = CL_{R,MER} \cdot \left(\frac{CL_{GFR}(t)}{6\,L/h} \right)^{\gamma} \qquad \textit{Equation 16}$$

The $CL_{R,MER}$ is the population mean renal clearance of meropenem for a patient with standard (6 L/h) CL_{GFR}. As the $CL_{GFR}(t)$ was time dependent, $CL_{R,MER}(t)$ was also time dependent. The exponent gamma (γ) can account for nonlinearity in the relationship between renal clearance of meropenem and CL_{GFR}. For an estimated γ below 1.0, $CL_{R,MER}$ increases less than linearly with CL_{GFR}.

Modeling of infection biomarkers

Similar to serum creatinine, the infection biomarkers C-reactive protein and procalcitonin were modeled as endogenous compounds using a one-compartment model to describe each biomarker (Figure 5-1). Patients with high concentrations of these biomarkers at 0 h were assumed to have an infection at initiation of therapy. For patients who developed an infection during therapy, we estimated the time of infection as well as the delay and extent of increase of the C-reactive protein and procalcitonin concentrations.

13.1.1.3. Population estimation methodology

Nonlinear mixed-effects modeling of all data simultaneously was performed via the importance sampling algorithm (pmethod=4) in S-ADAPT (version 1.57)[97]. We utilized the SADAPT-TRAN facilitator tool for pre- and post-processing[98,99]. Between patient variability was described by log-normal distributions of all model parameters and residual error was described by an additive plus proportional model for each dependent variable. Model evaluation and selection was performed via standard population modeling procedures[100]. Descriptive statistics were calculated in WinNonlin Professional® (version 5.3, Pharsight, Cary, NC).

13.1.1.4. Statistical analysis

Fisher's exact test was used in the GraphPad Prim software (version 6.05, La Jolla, CA) to assess, whether dose adjustment led to an improved probability of achieving meropenem trough concentrations within the targeted range of 2 to 16 mg/L.

Table 13-1 Population pharmacokinetic parameter estimates for meropenem, serum creatinine, C-reactive protein (CRP) and procalcitonin (PCT).

	Symbol	Unit	Population mean (relative standard error, SE%)	Between subject variability (SE%)
Volume of distribution of the central compartment	V_1	L	27.2 [a] (6.3%)	0.248 (64.2%)
Glomerular filtration fraction for creatinine	F_{Filt}		0.979 (5.9%)	0.331 (43.7%)
Meropenem renal clearance in patients with normal renal function	$CL_{R,MER}$	L/h	9.86 [a,b] (6.2%)	0.380 (22.5%)
Meropenem nonrenal clearance	$CL_{NR,MER}$	L/h	0.480 [a] (21.5%)	0.226 (161%)
Exponent of relationship between clearance of meropenem and creatinine	γ		0.593 (14.5%)	0.100 (fixed)
Time of first change of renal function	T1	h	40.7 (8.6%)	0.247 (251%)
Time between first and second change of renal function	T2-T1	h	73.8 (7.7%)	0.292 (122%)
Ratio of renal function after the first change compared to baseline at 0 h	RF1		Sepsis: 1.05 (6.9%) No Sepsis: 1.04 (3.8%)	0.329 (80.6%) 0.041 (236%)
Ratio of renal function after the 2nd change compared to baseline at 0 h	RF2		Sepsis: 1.23 (14.1%) No Sepsis: 1.26 (2.9%)	0.675 (36.4%) 0.023 (189%)
Half-life for the rate of change of renal function	$t1/2_{RF}$	h	0.516 (7.3%)	0.119 (183%)
Concentration of CRP at 0 h	IC_{CRP}	mg/dL	13.9 (11.6%)	0.800 (23.0%)
Concentration of PCT at 0 h	IC_{PCT}	ng/mL	2.51 (41.1%)	2.49 (24.3%)
Half-life of turnover of CRP	$t1/2_{CRP}$	h	93.1 (10.8%)	0.661 (29.3%)
Half-life of turnover of PCT	$t1/2_{PCT}$	h	46.9 (11.2%)	0.280 (133%)
Modeled time of infection	T_{Infect}	h	22.6 (25.1%)	1.41 (30.9%)
Delay time between modeled time of infection and rise of CRP and PCT	$T_{Rise,Inf}$	h	26.6 (16.7%)	0.646 (68.5%)
Increase of CRP due to infection	ΔCRP_{INF}	mg/dL	20.0 (10.6%)	0.425 (91.3%)
Increase of PCT due to infection	ΔPCT_{INF}	ng/mL	5.11 (49.7%)	1.16 (46.5%)

[a]: For a patient of normal body size (i.e. 70 kg total body weight).
[b]: Normalized to a creatinine clearance of 6.0 L/h (equivalent to 100 mL/min).

The additive and proportional residual errors were 0.358 mg/L and 20.7% for meropenem in plasma, 0.00921 mg/dL and 11.1% for serum creatinine, 0.147 mg/dL and 15.4% for C-reactive protein, and 0.0140 ng/mL and 28.7% for procalcitonin.

13.2. Supplementary information on chapter 6 - Pharmacokinetics and bone penetration of ampicillin and sulbactam in patients undergoing total hip replacement surgery

13.2.1. Graphical representation of the determination of the elimination rate constants (ke)

Figure 13-1 Determination of ke of ampicillin in plasma in group 1, patient 5.

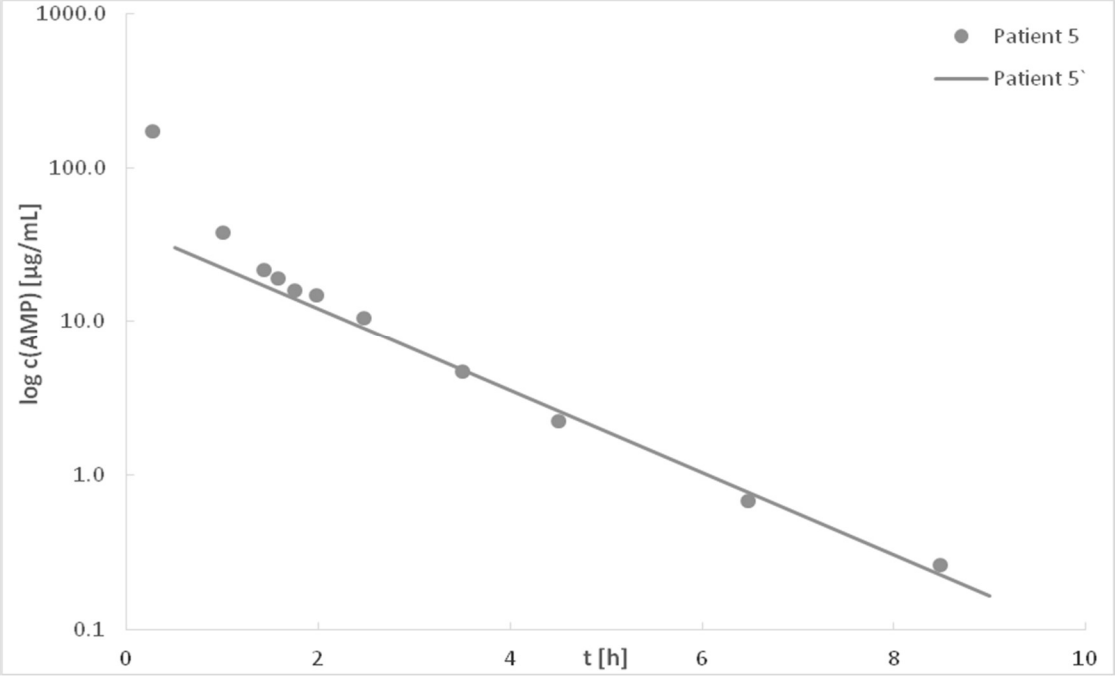


Figure 13-2 Determination of ke of sulbactam in plasma in group 1, patient 5.

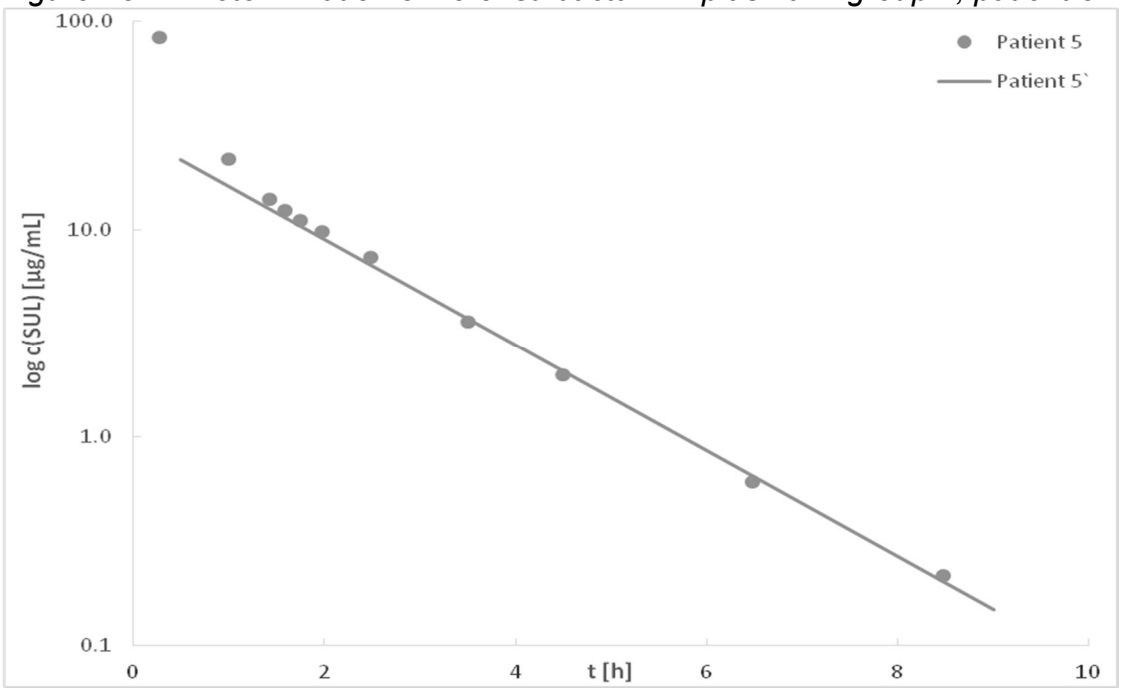


Figure 13-3 Determination of ke of ampicillin in plasma in group 1, patient 9.

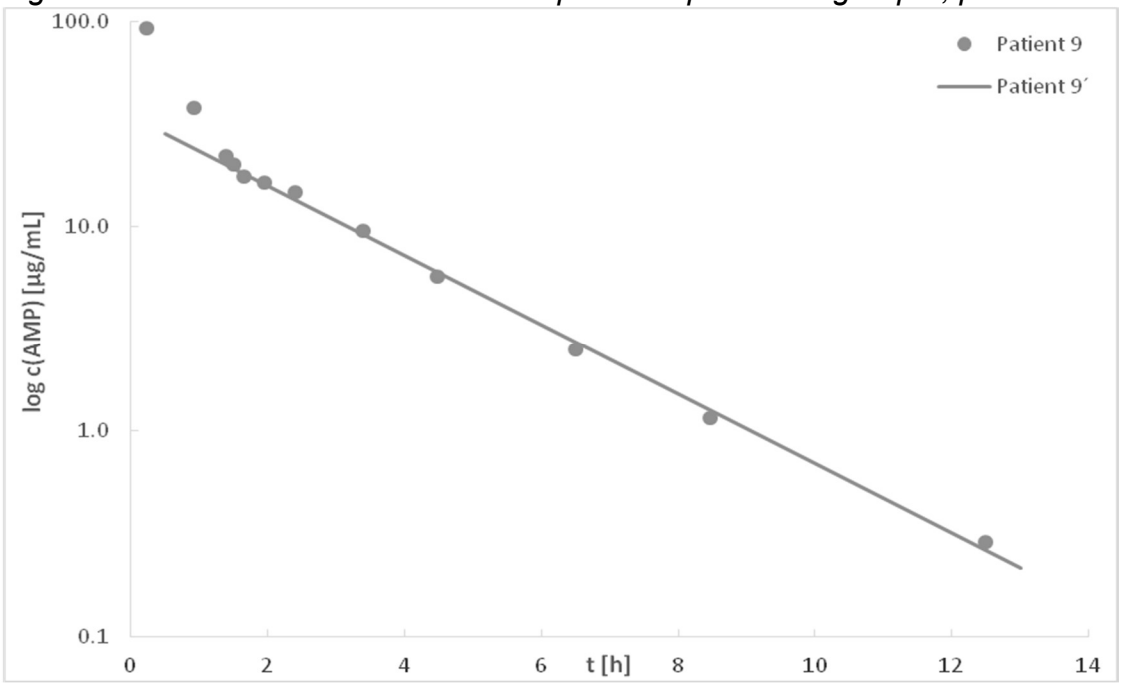


Figure 13-4 Determination of ke of sulbactam in plasma in group 1, patient 9.

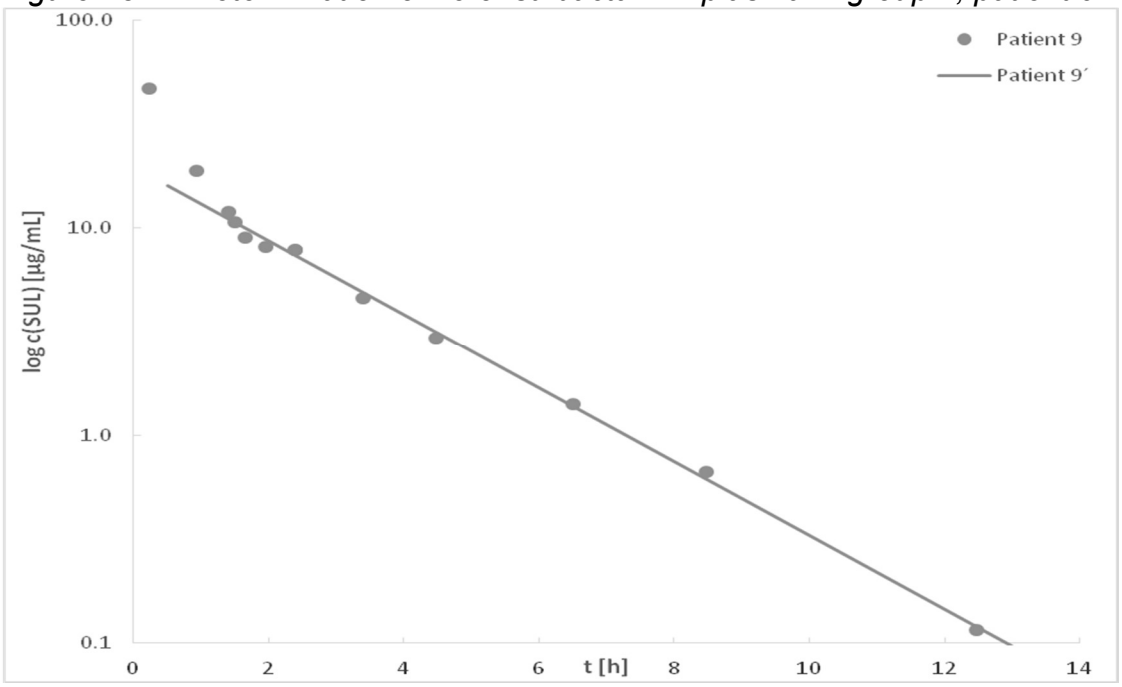


Figure 13-5 Determination of ke of ampicillin in plasma in group 1, patient 14.

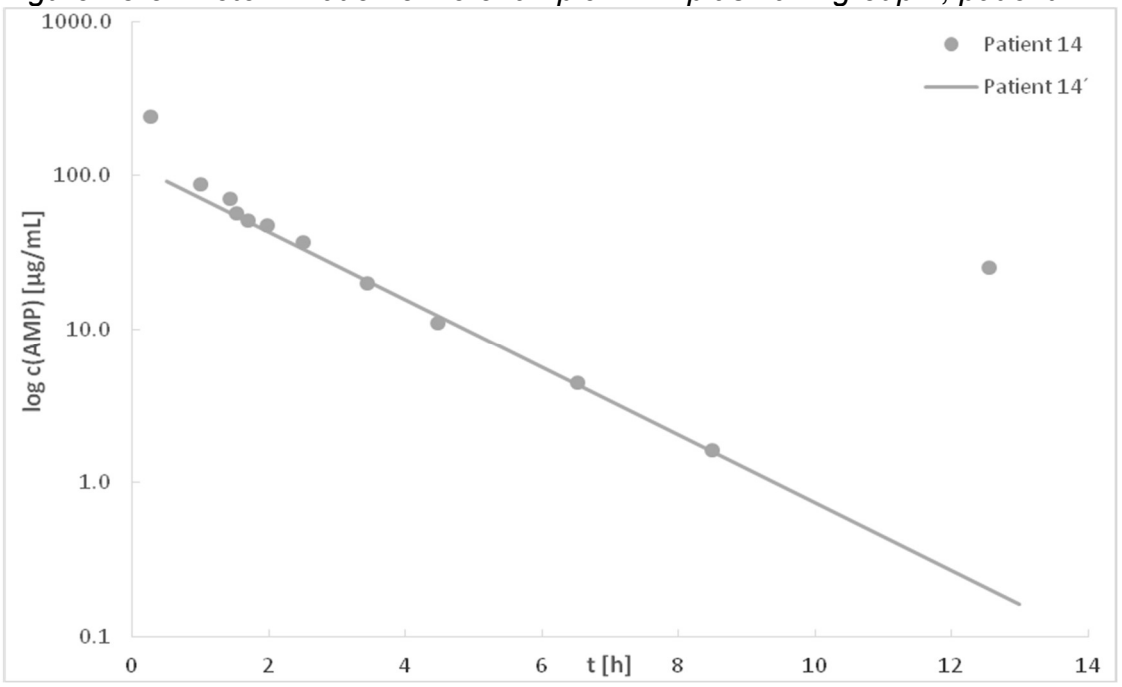


Figure 13-6 Determination of ke of sulbactam in plasma in group 1, patient 14.

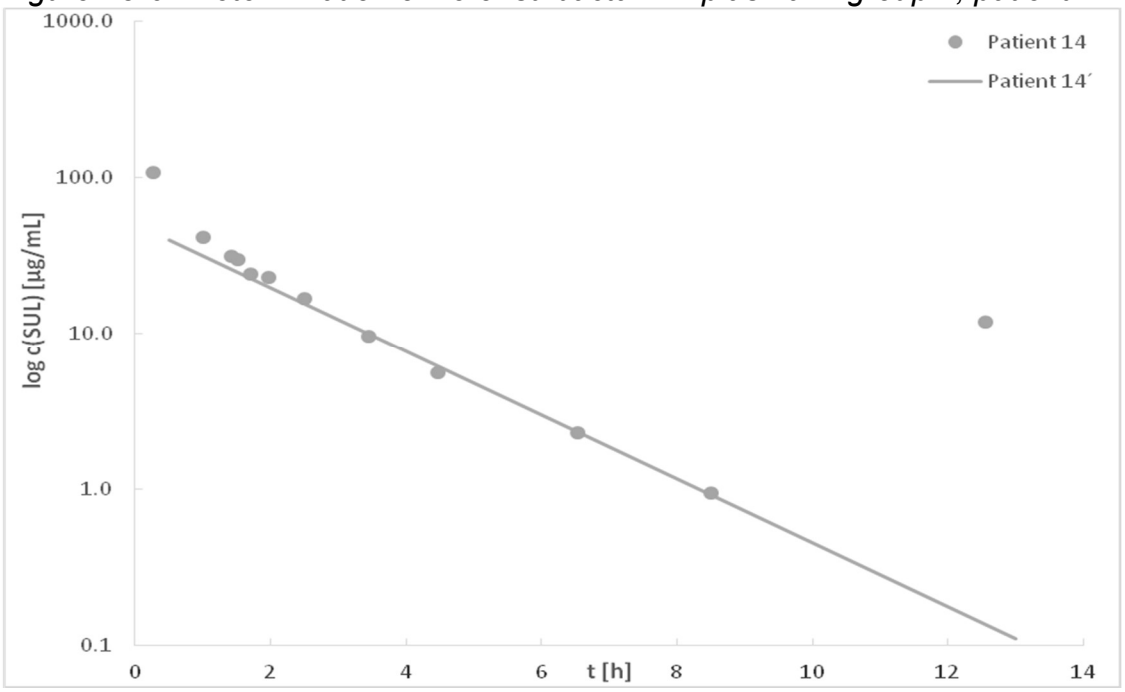


Figure 13-7 Determination of ke of ampicillin in plasma in group 1, patient 16.

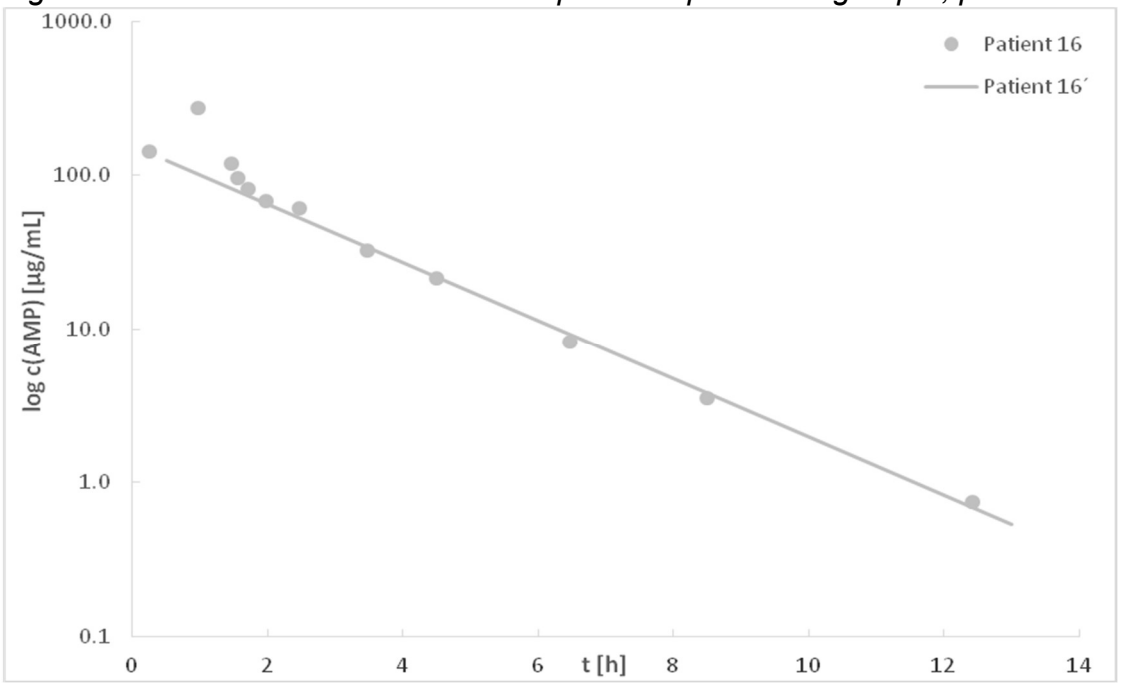


Figure 13-8 Determination of ke of sulbactam in plasma in group 1, patient 16.

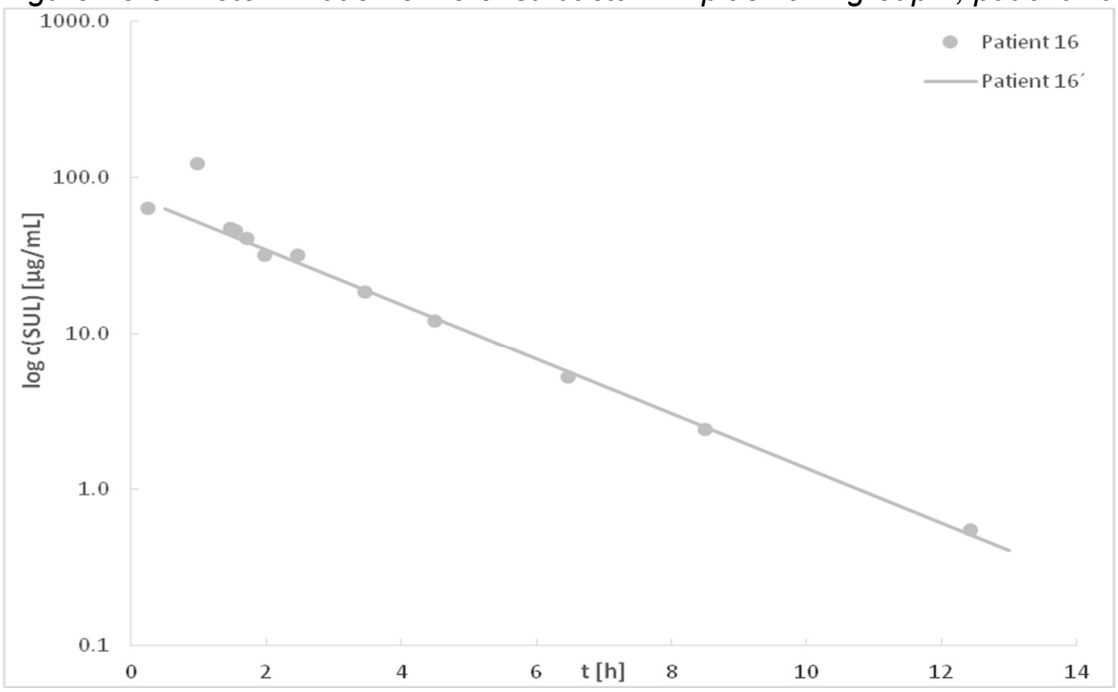


Figure 13-9 Determination of ke of ampicillin in plasma in group 2, patient 1.

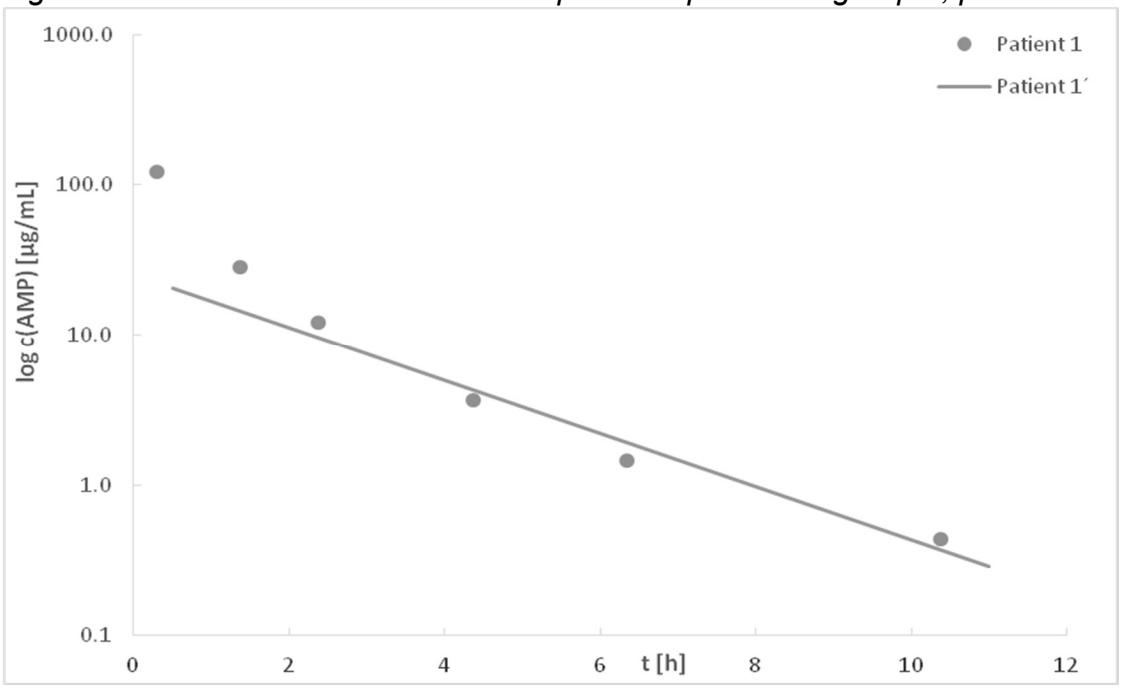


Figure 13-10 Determination of ke of sulbactam in plasma in group 2, patient 1.

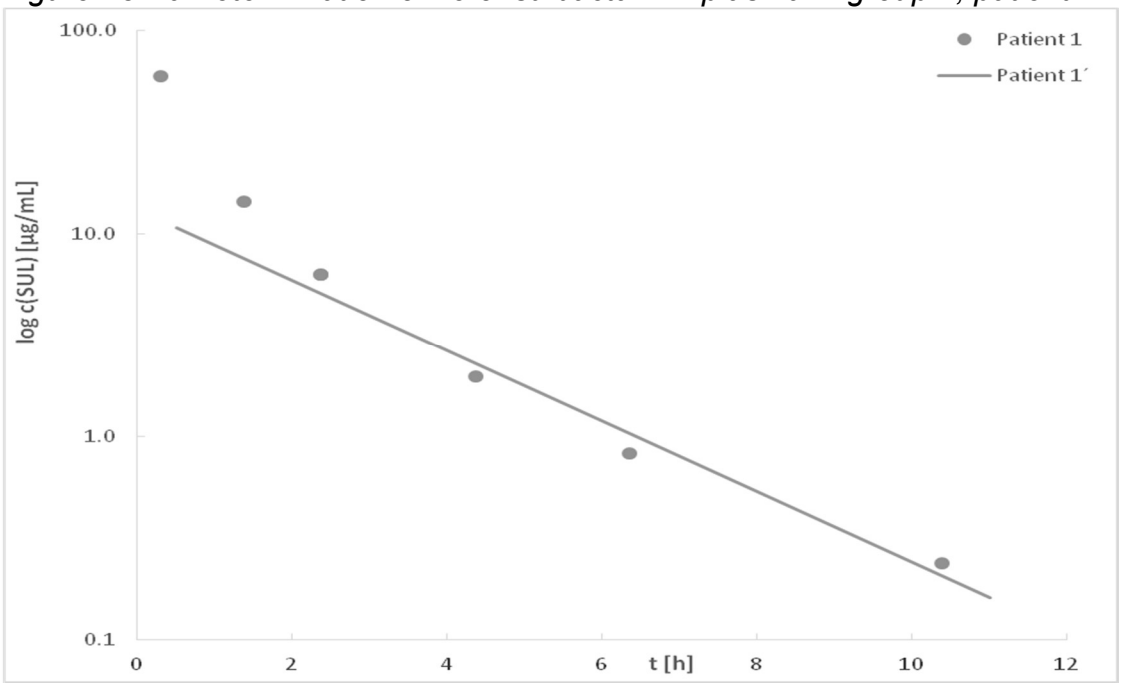


Figure 13-11 Determination of ke of ampicillin in plasma in group 2, patient 7.

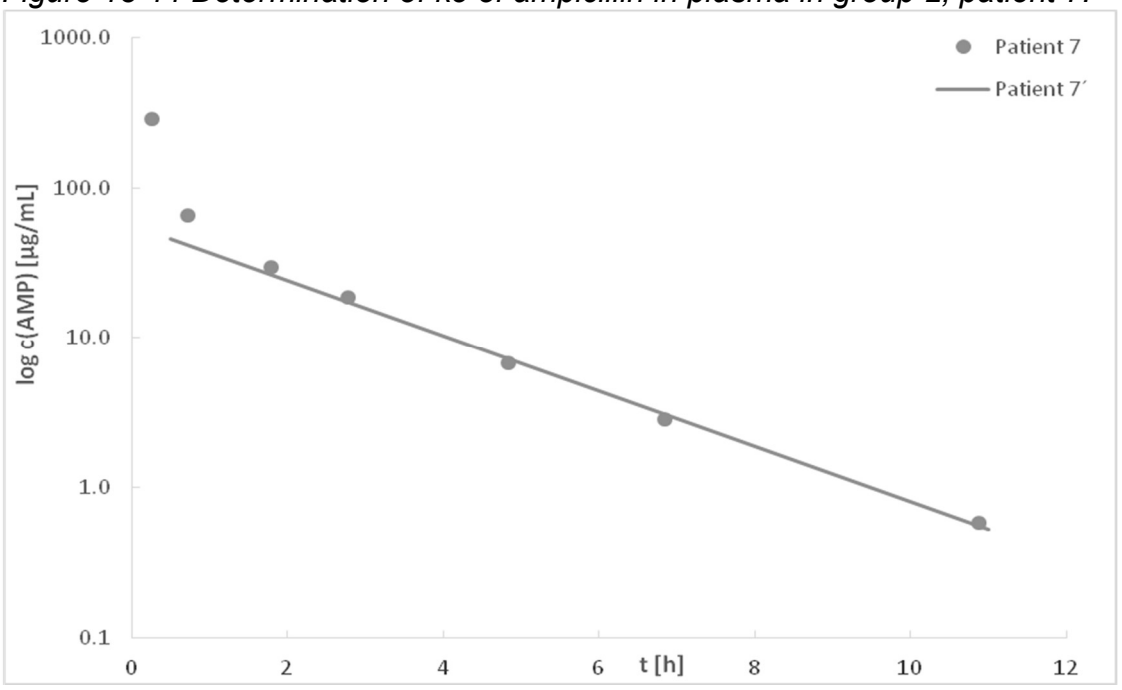


Figure 13-12 Determination of ke of sulbactam in plasma in group 2, patient 7.

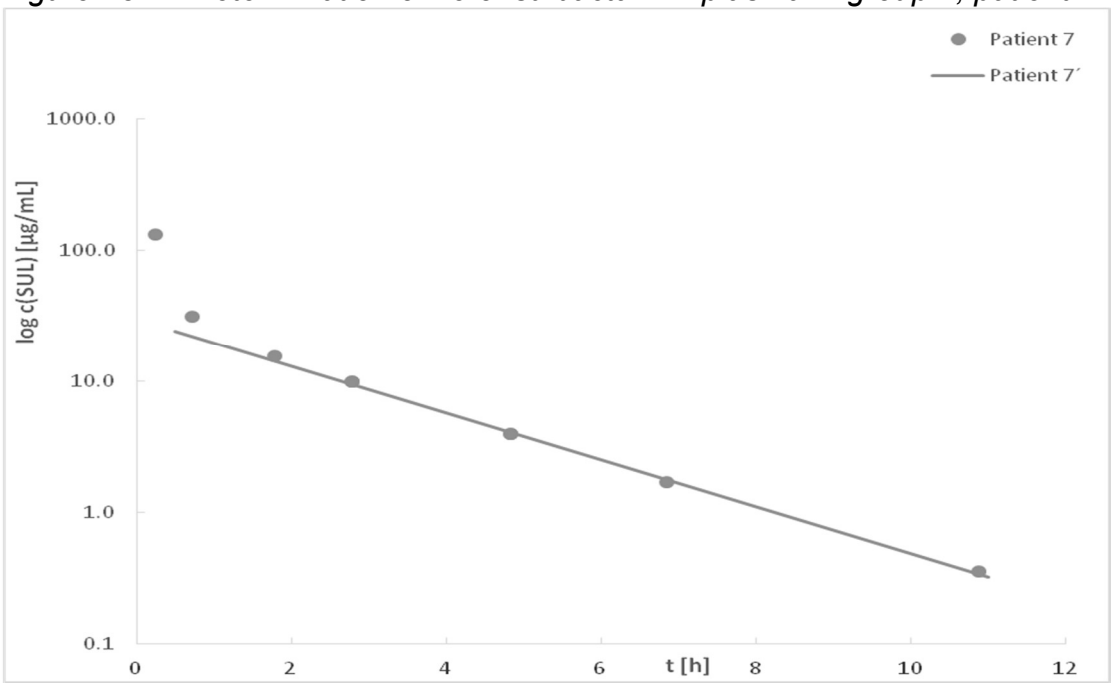


Figure 13-13 Determination of ke of ampicillin in plasma in group 2, patient 13.

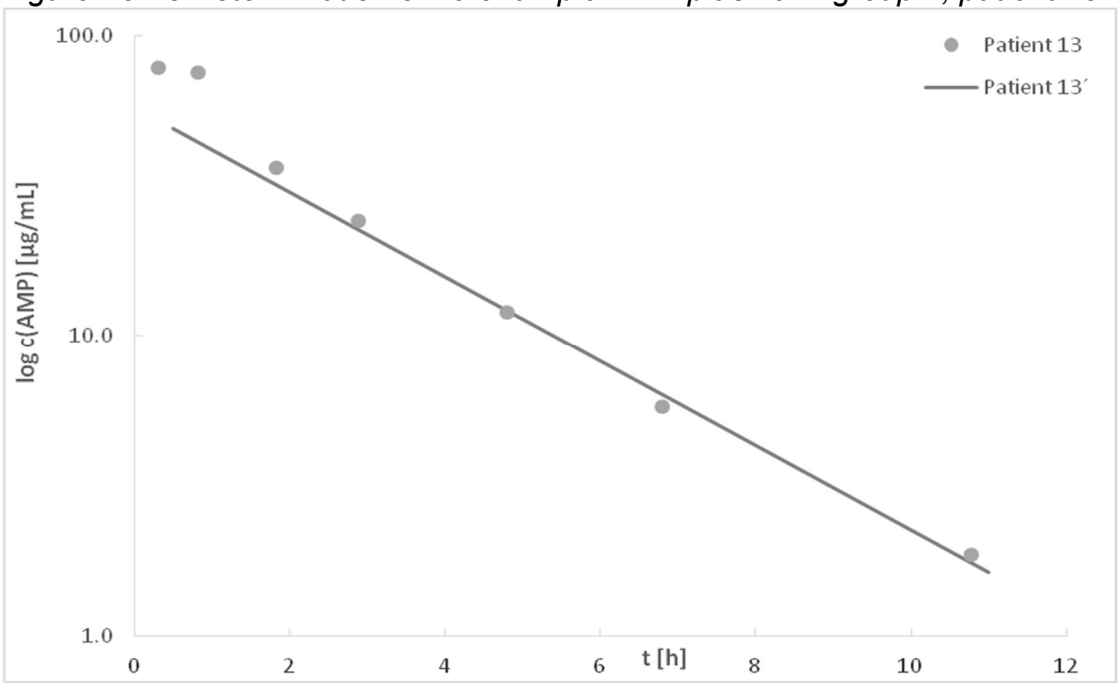


Figure 13-14 Determination of ke of sulbactam in plasma in group 2, patient 13.

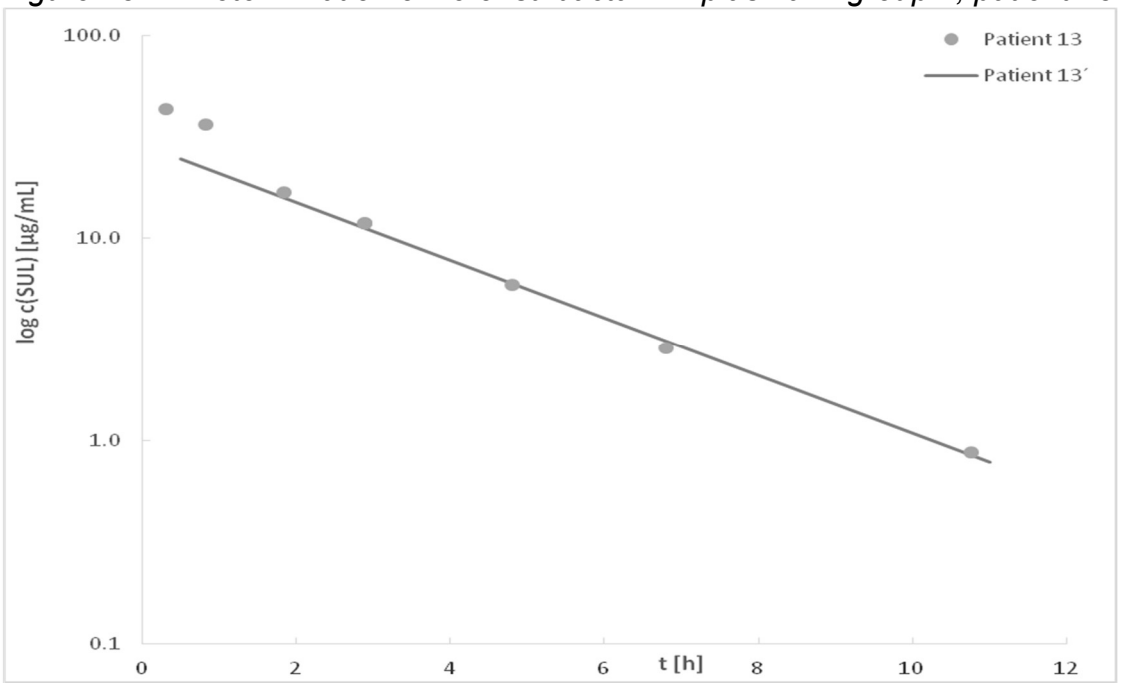


Figure 13-15 Determination of ke of ampicillin in plasma in group 2, patient 20.

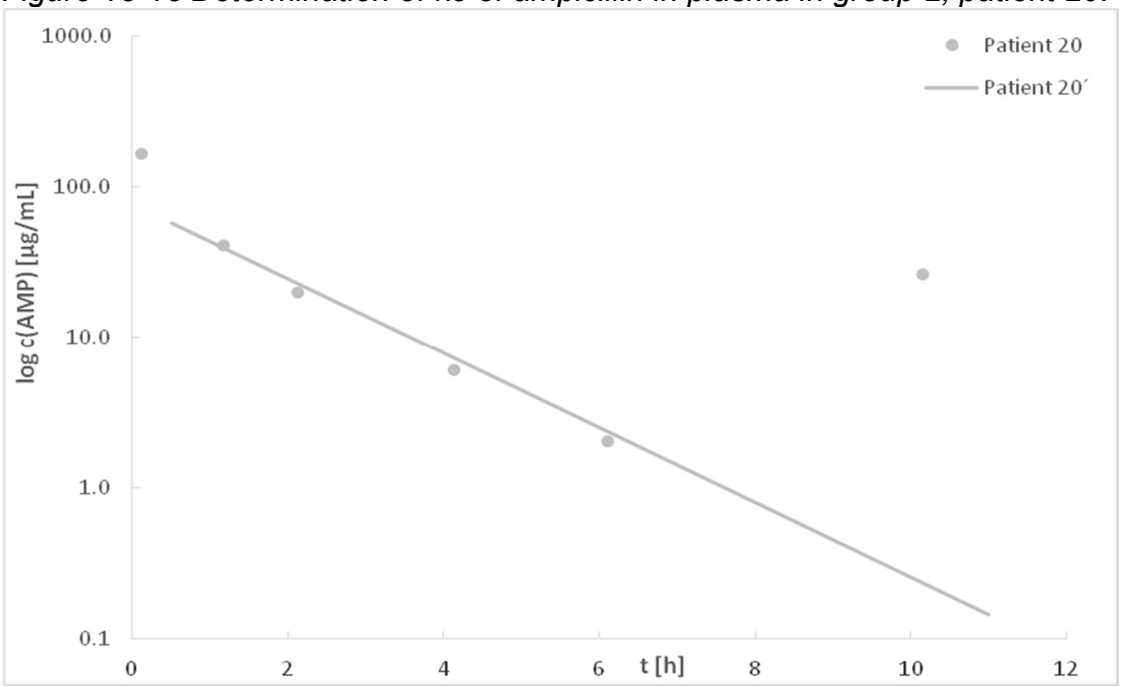


Figure 13-16 Determination of ke of sulbactam in plasma in group 2, patient 20.

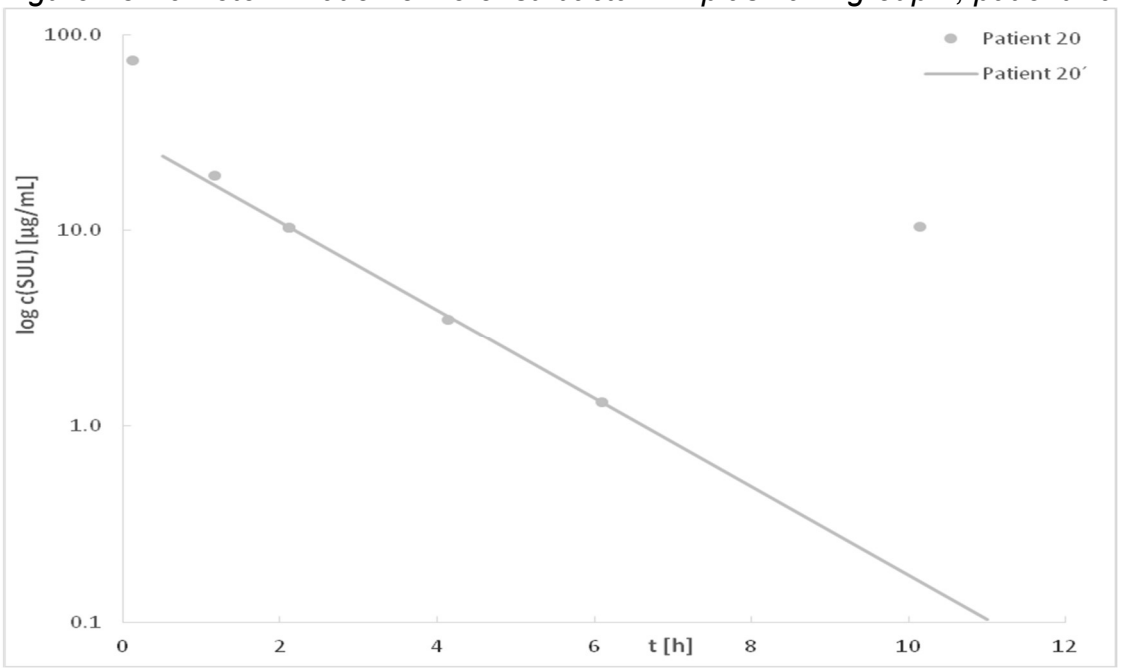


Figure 13-17 Determination of ke of ampicillin in plasma in group 3, patient 3.

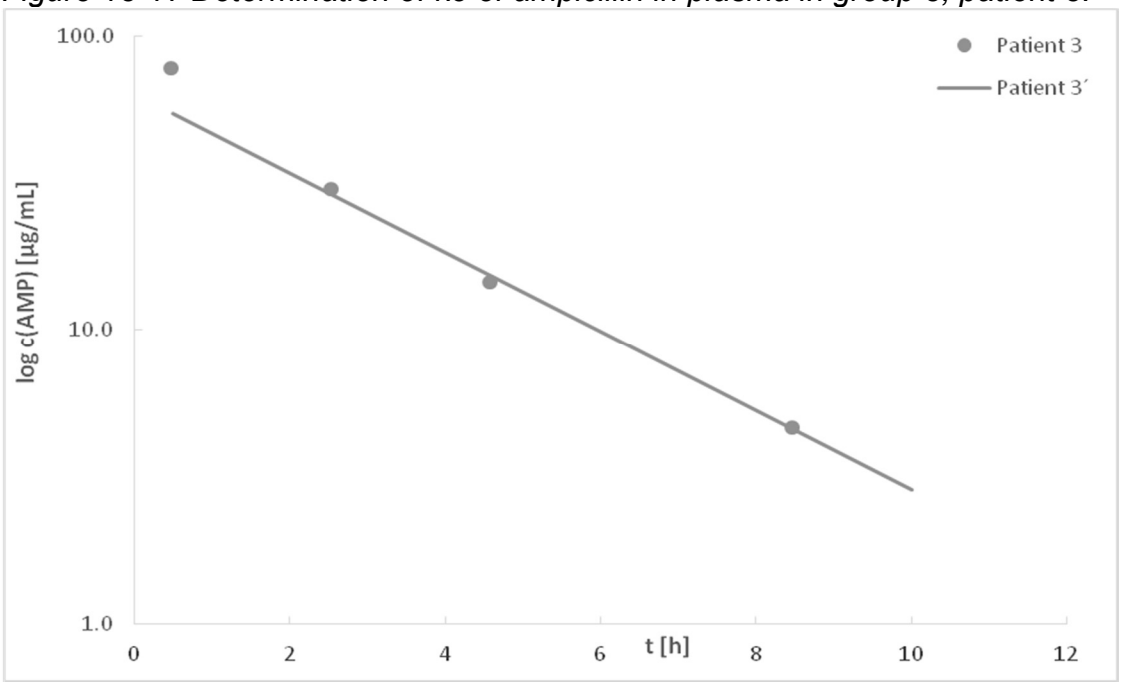


Figure 13-18 Determination of ke of sulbactam in plasma in group 3, patient 3.

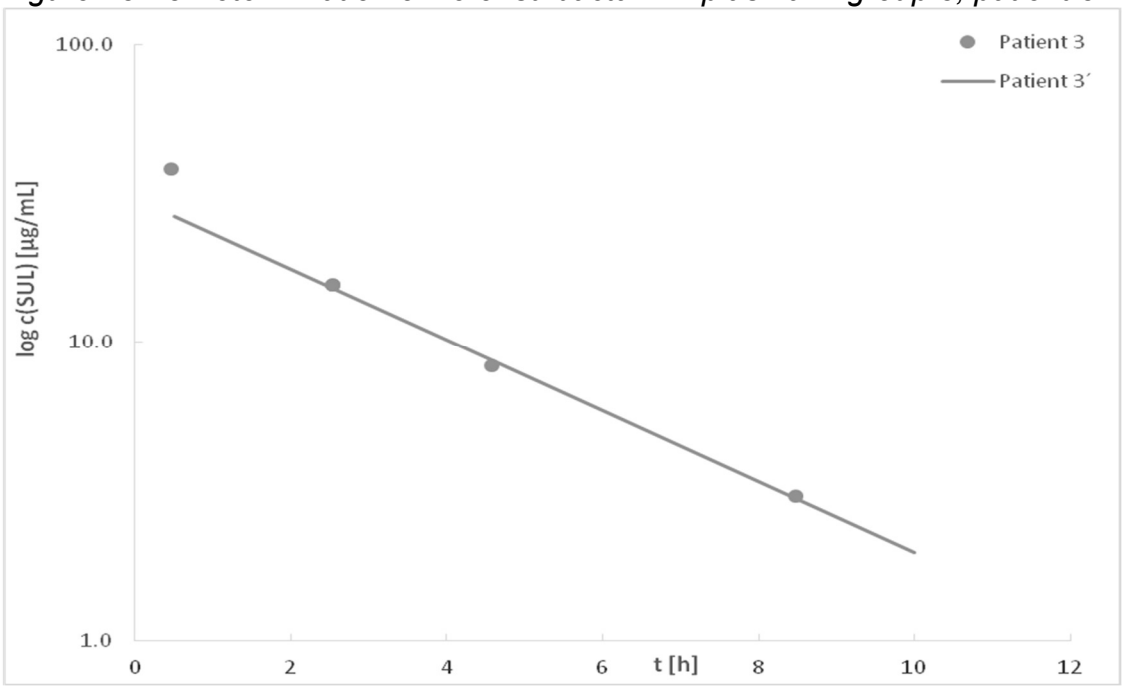


Figure 13-19 Determination of ke of ampicillin in plasma in group 3, patient 6.

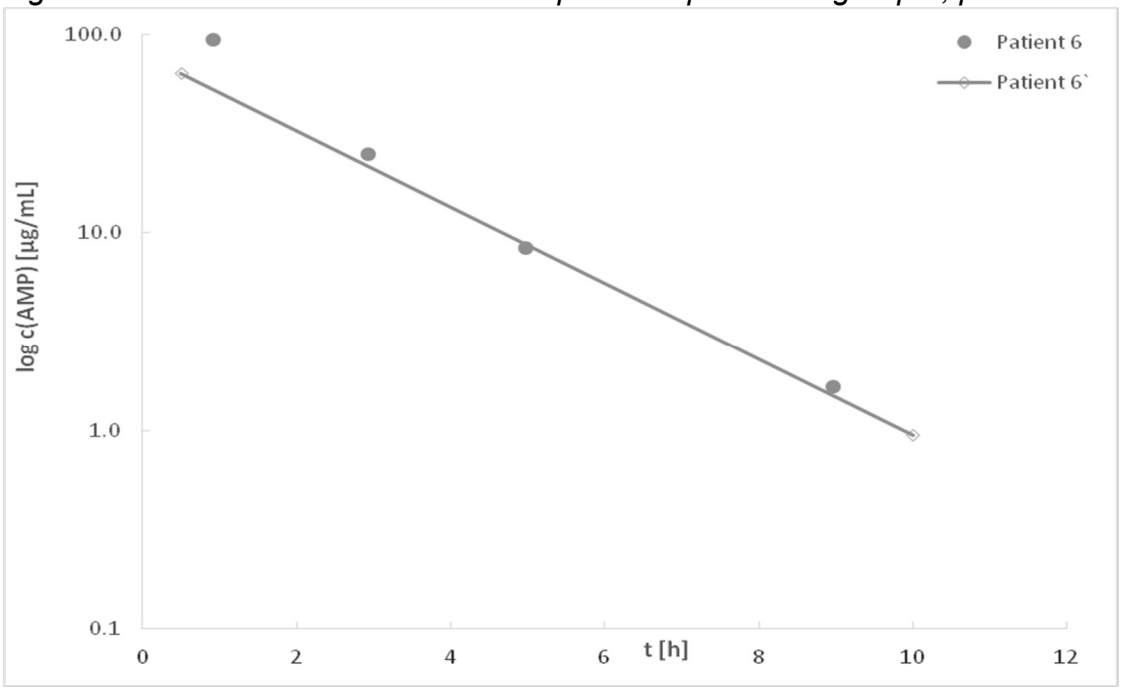


Figure 13-20 Determination of ke of sulbactam in plasma in group 3, patient 6.

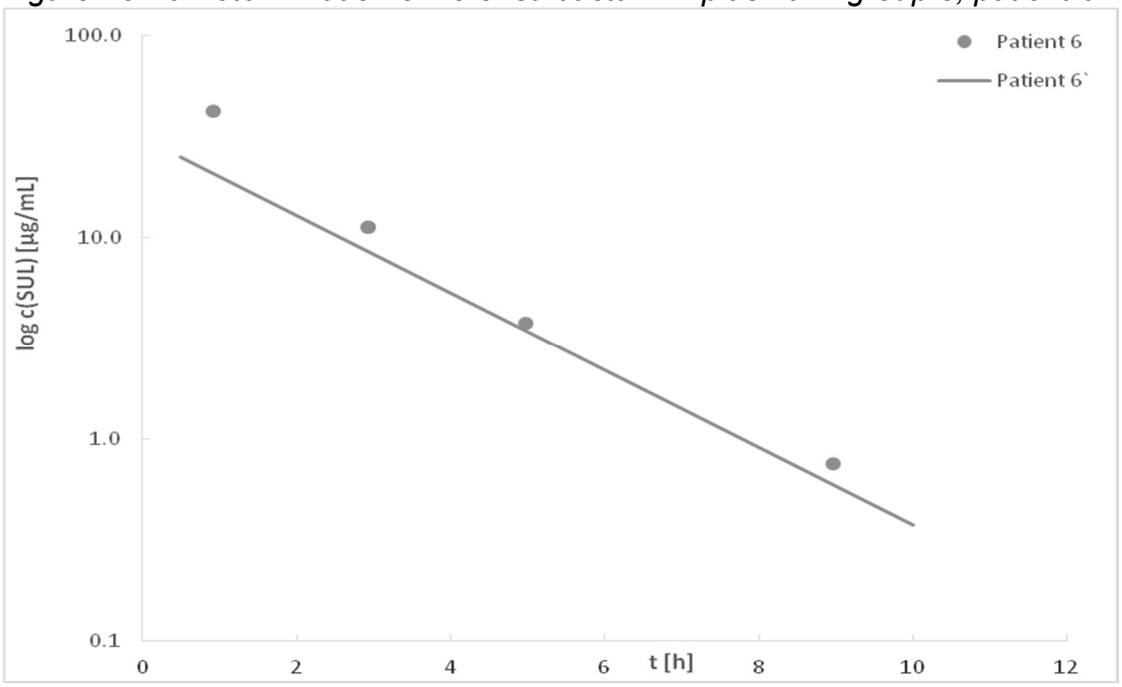


Figure 13-21 Determination of ke of ampicillin in plasma in group 3, patient 12.

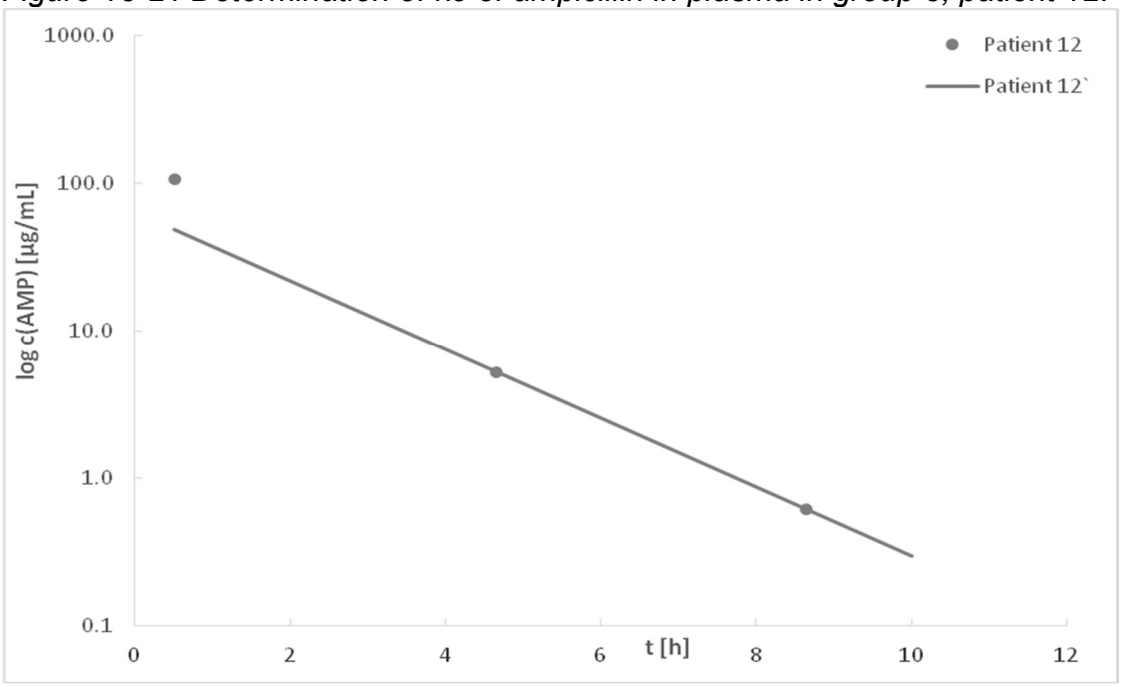


Figure 13-22 Determination of ke of sulbactam in plasma in group 3, patient 12.

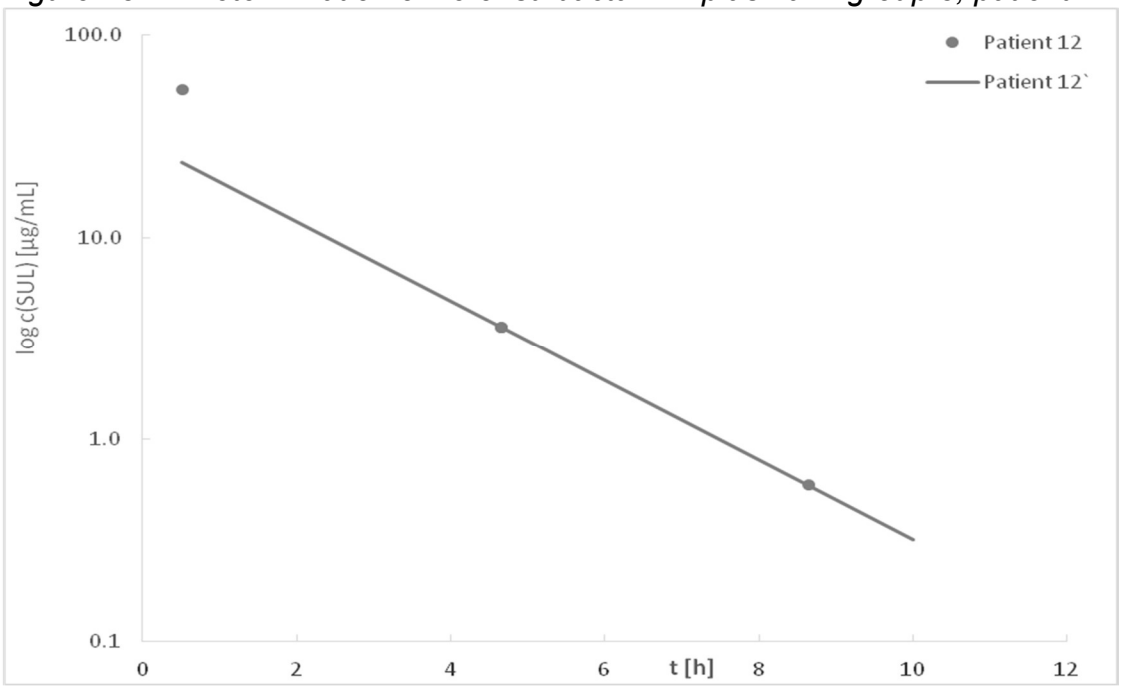


Figure 13-23 Determination of ke of ampicillin in plasma in group 3, patient 19.

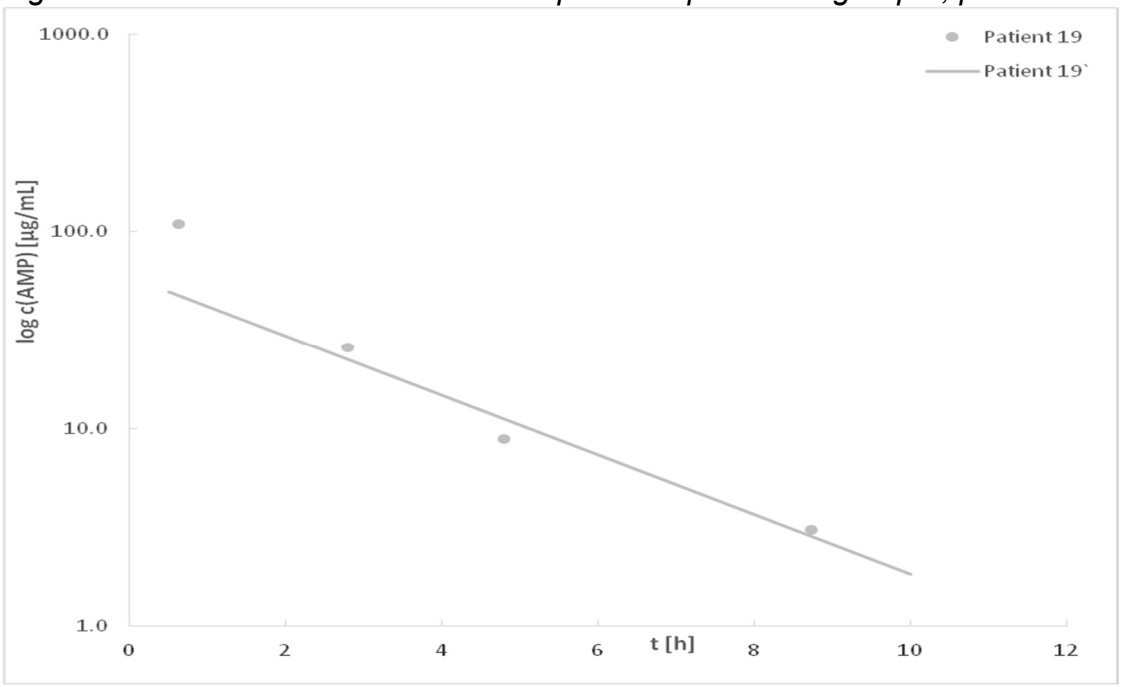


Figure 13-24 Determination of ke of sulbactam in plasma in group 3, patient 19.

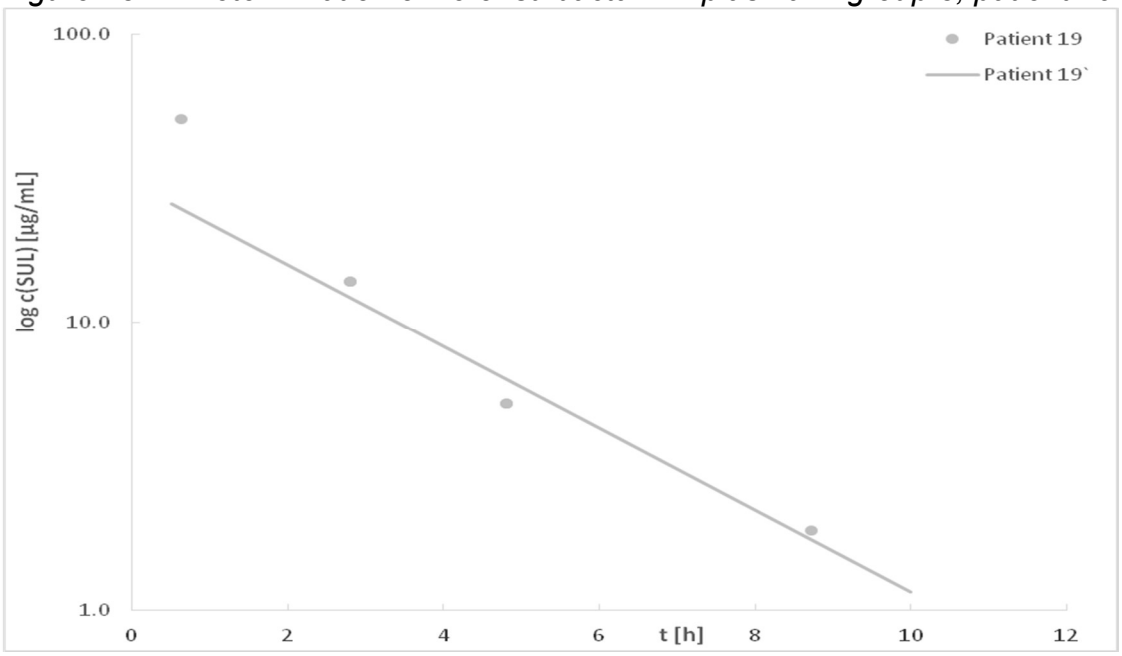


Figure 13-25 Determination of ke of ampicillin in plasma in group 4, patient 4.

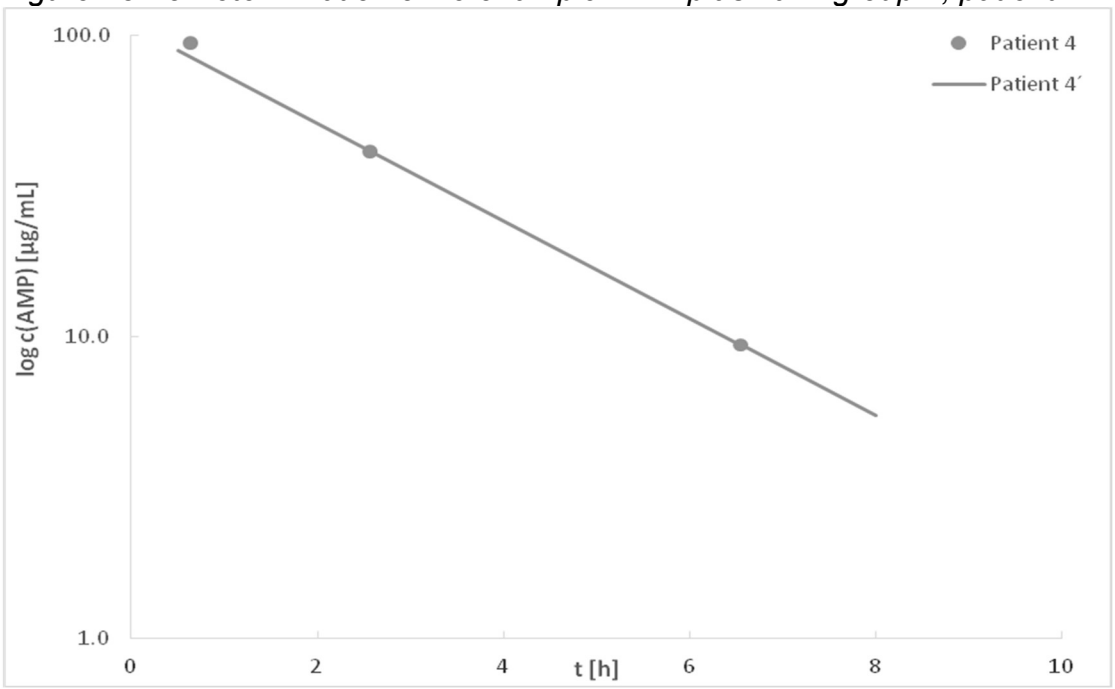


Figure 13-26 Determination of ke of sulbactam in plasma in group 4, patient 4.

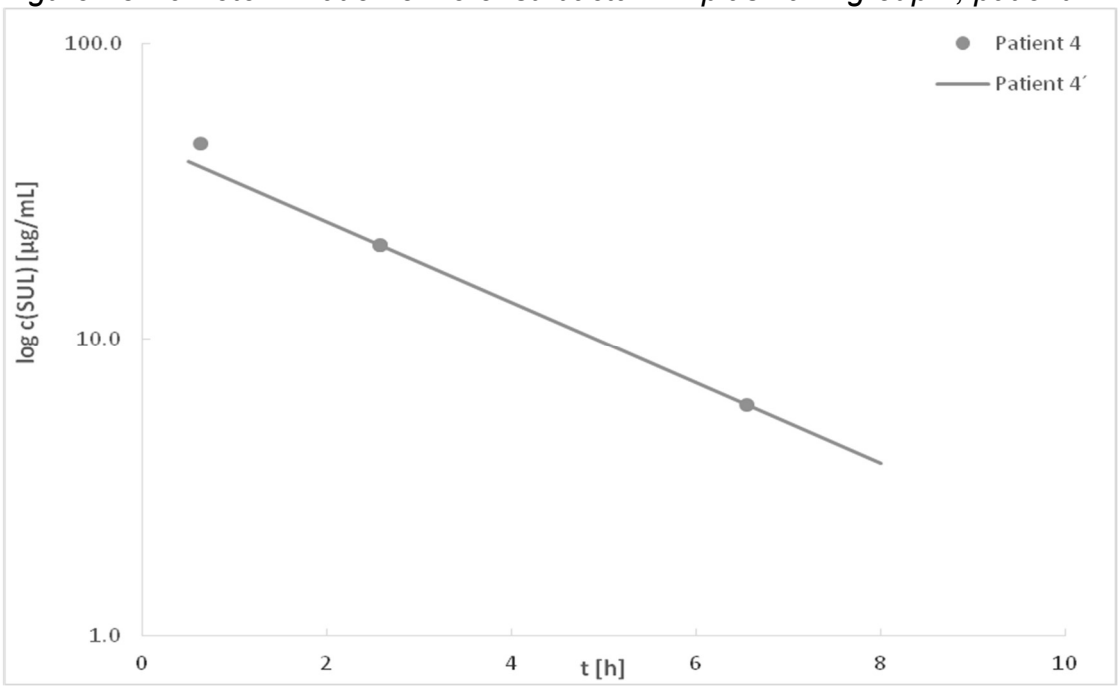


Figure 13-27 Determination of ke of ampicillin in plasma in group 4, patient 8.

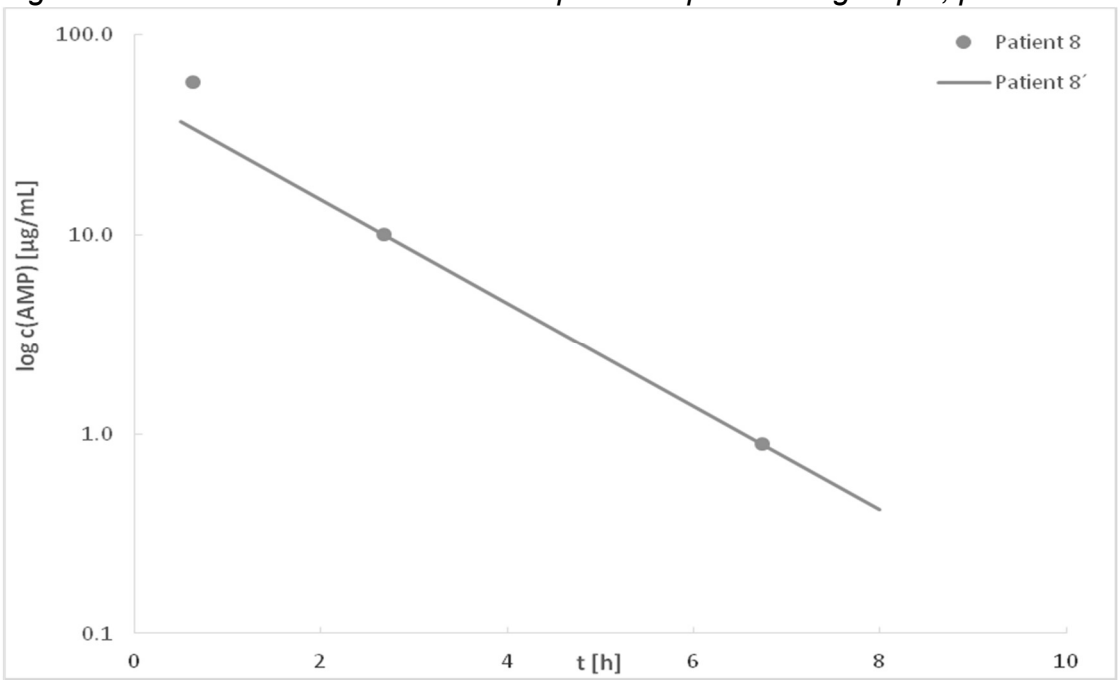


Figure 13-28 Determination of ke of sulbactam in plasma in group 4, patient 8.

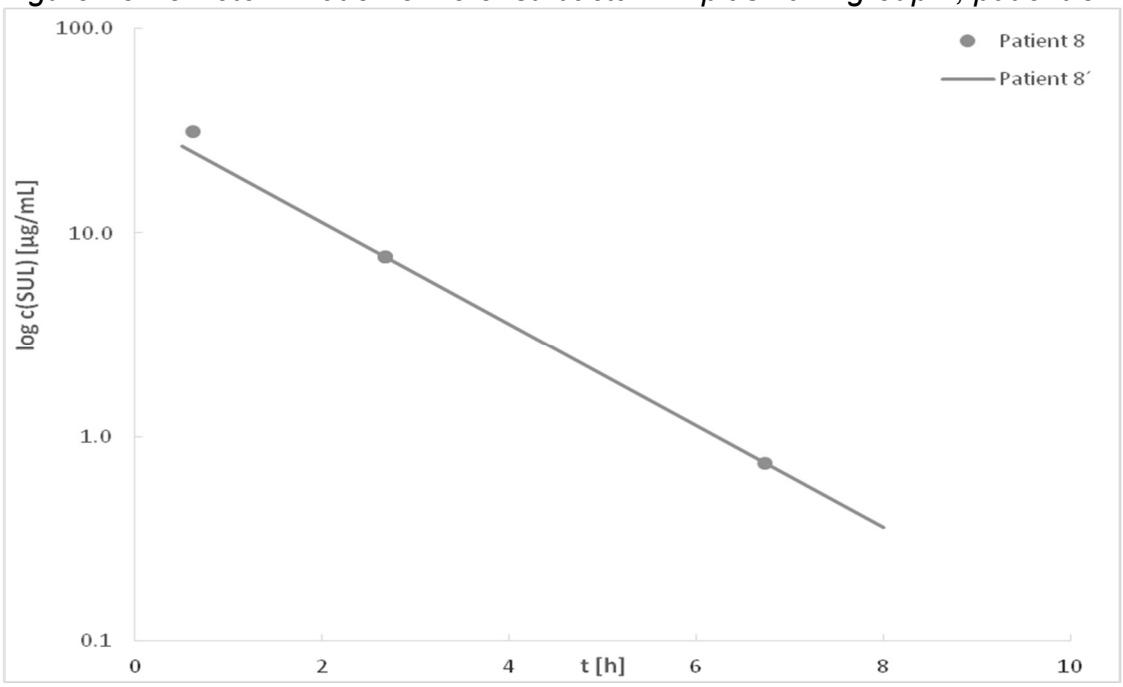


Figure 13-29 Determination of ke of ampicillin in plasma in group 4, patient 15.

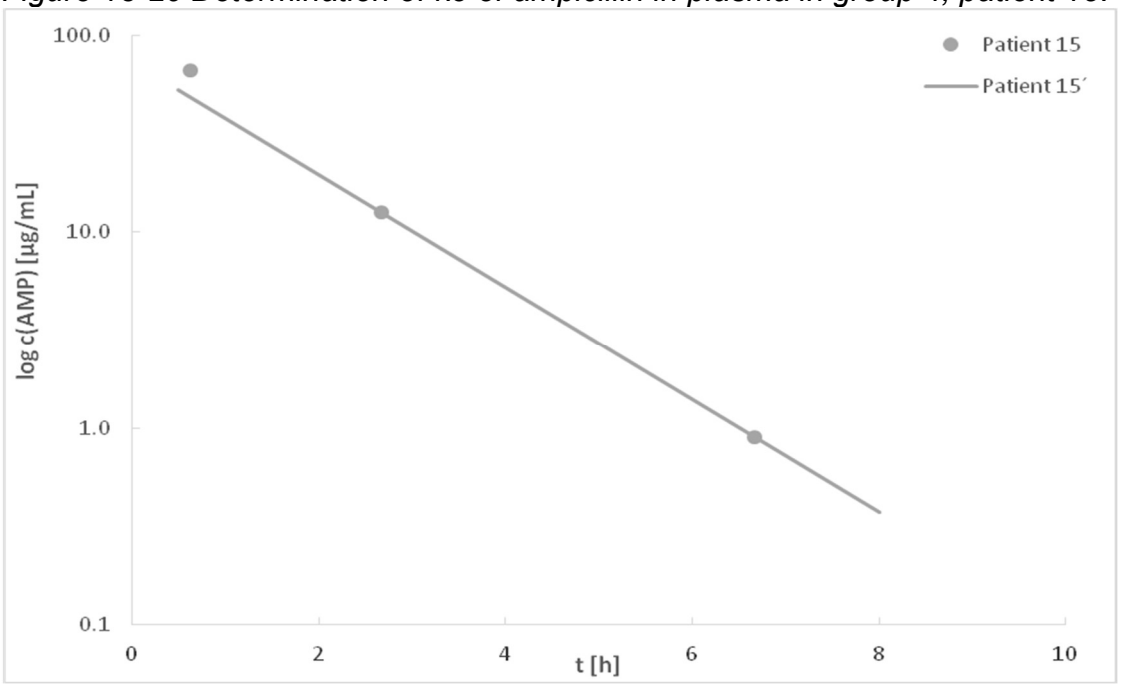


Figure 13-30 Determination of ke of sulbactam in plasma in group 4, patient 15.

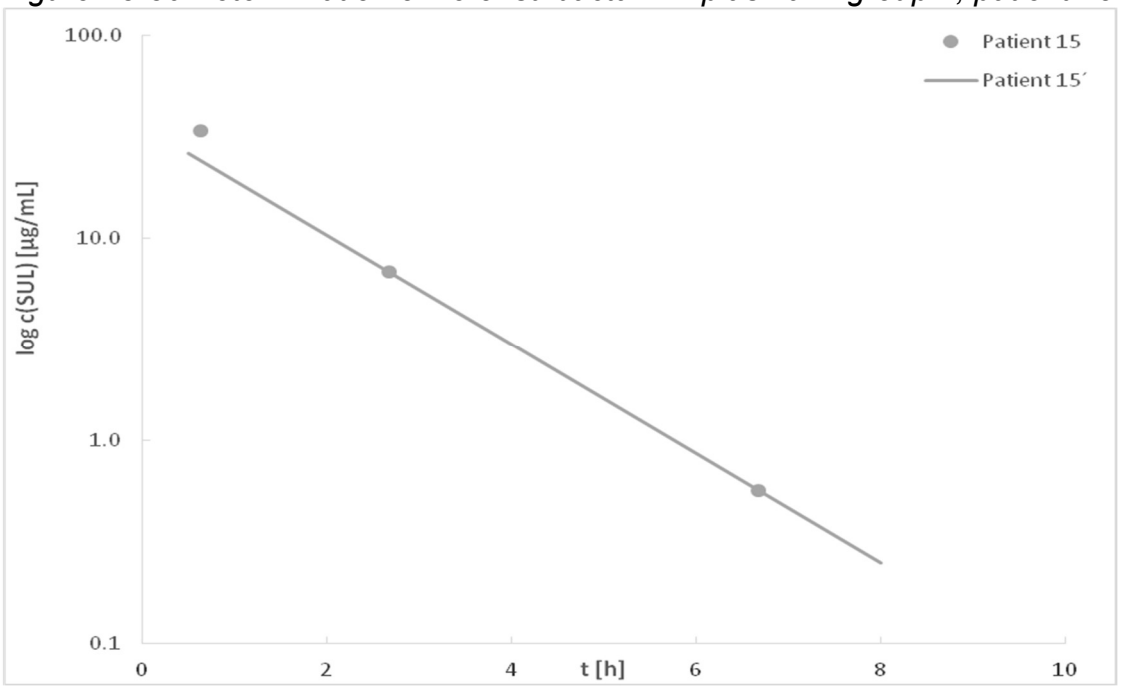


Figure 13-31 Determination of ke of ampicillin in plasma in group 4, patient 17.

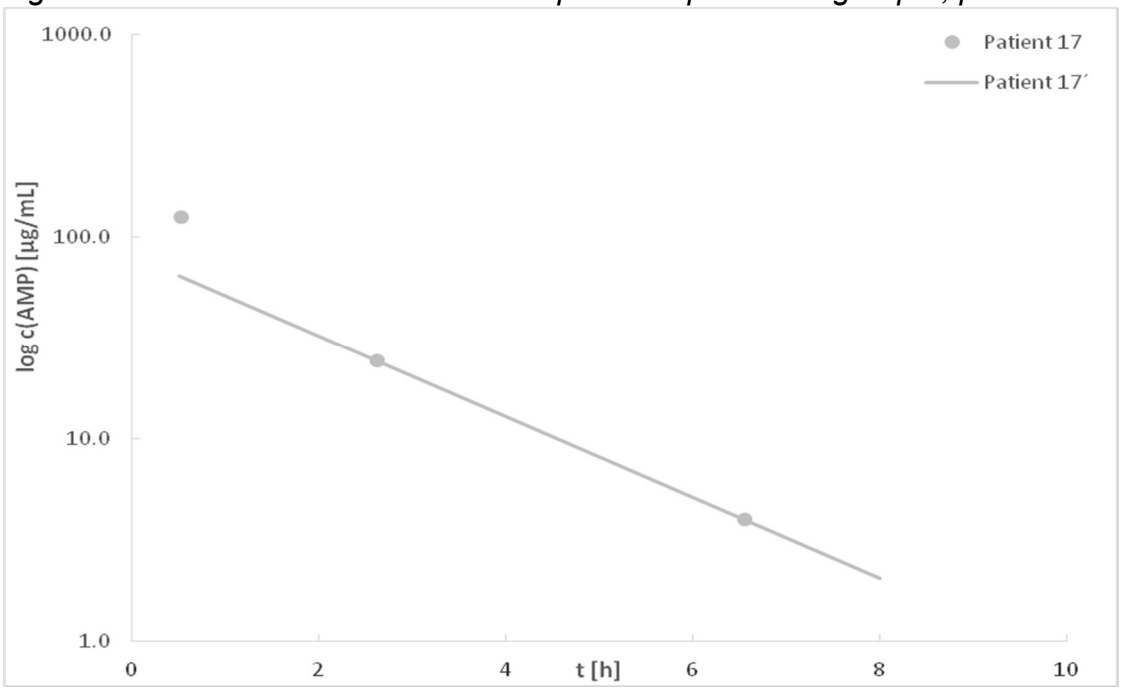
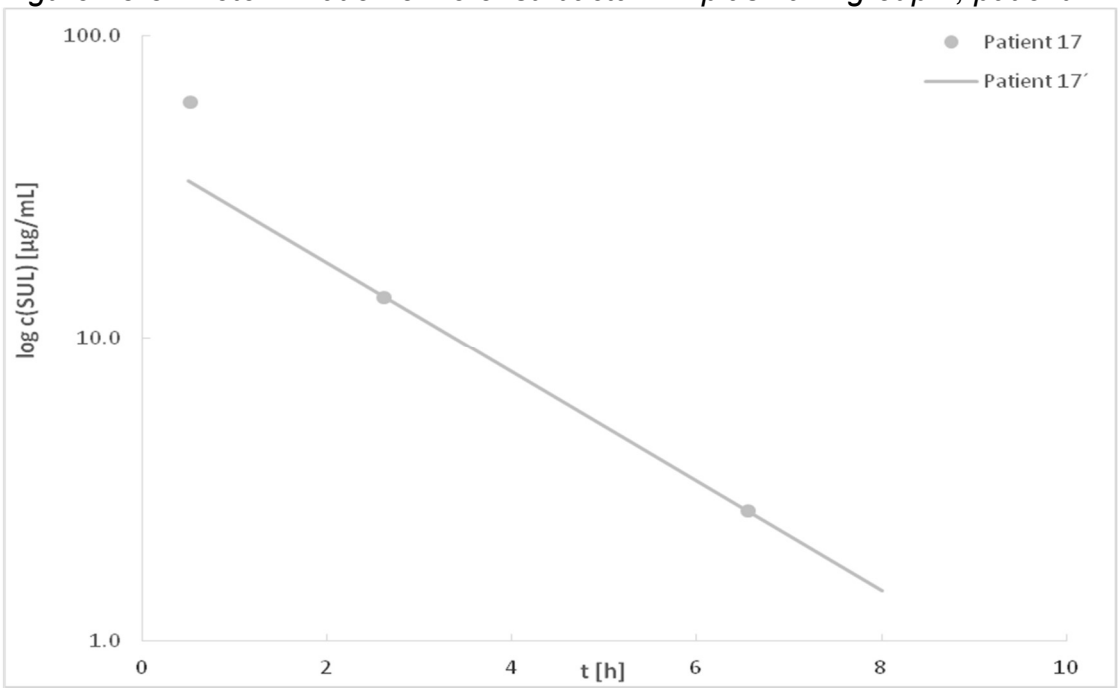


Figure 13-32 Determination of ke of sulbactam in plasma in group 4, patient 17.



13.2.2. Correlations of clearance and volume of distribution of ampicillin and sulbactam with demographical data

Figure 13-33 Correlation plot of ampicillin clearance and creatinine clearance.

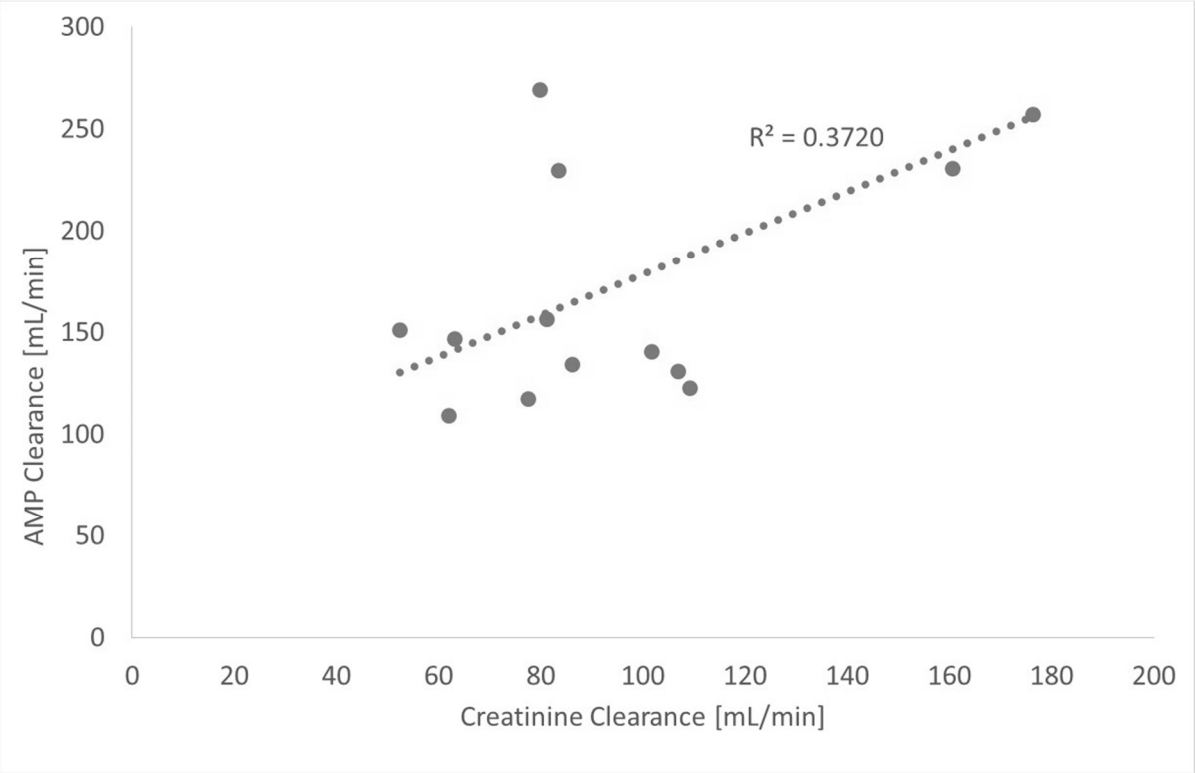


Figure 13-34 Correlation plot of sulbactam clearance and creatinine clearance.

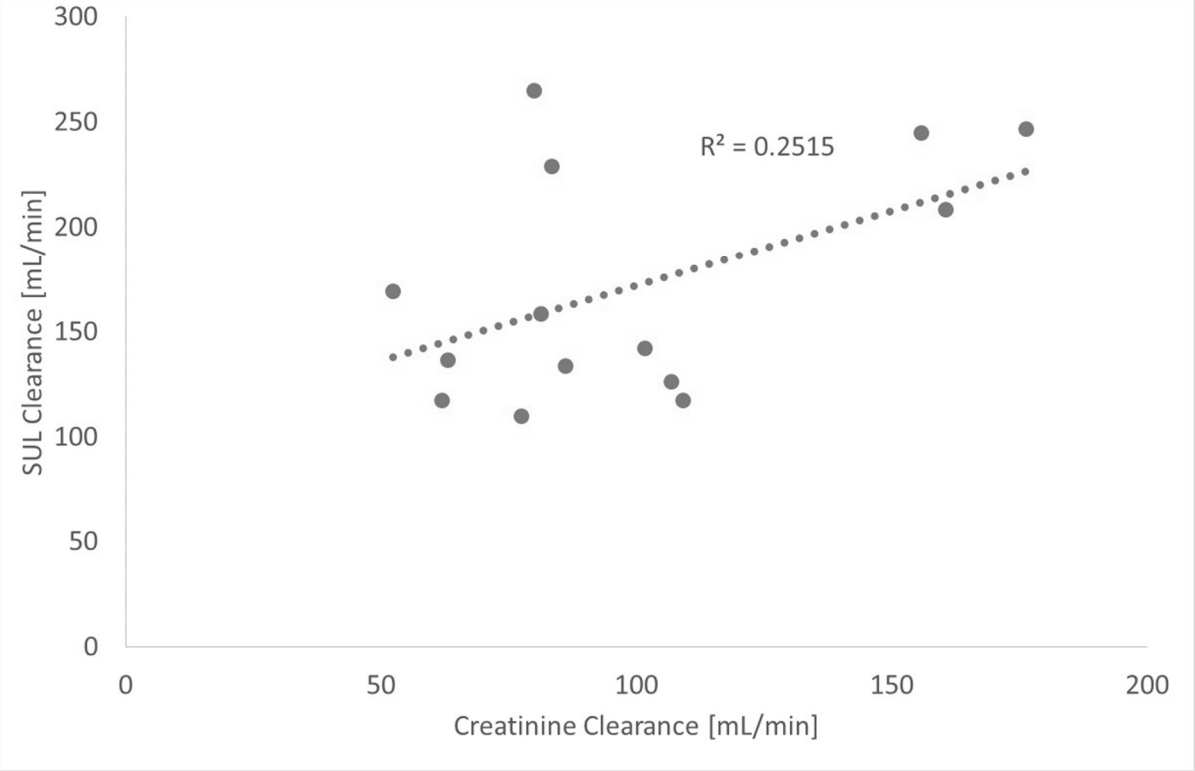


Figure 13-35 Correlation plot of ampicillin clearance and serum creatinine.

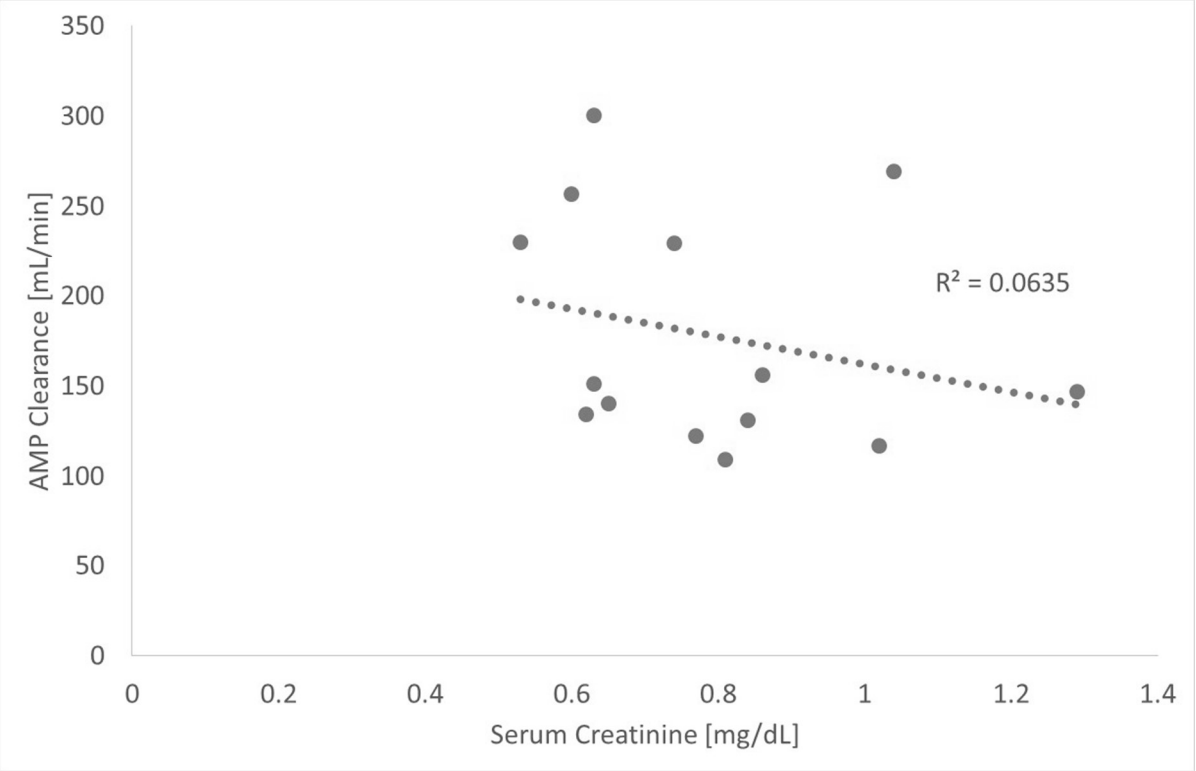


Figure 13-36 Correlation plot of sulbactam clearance and serum creatinine.

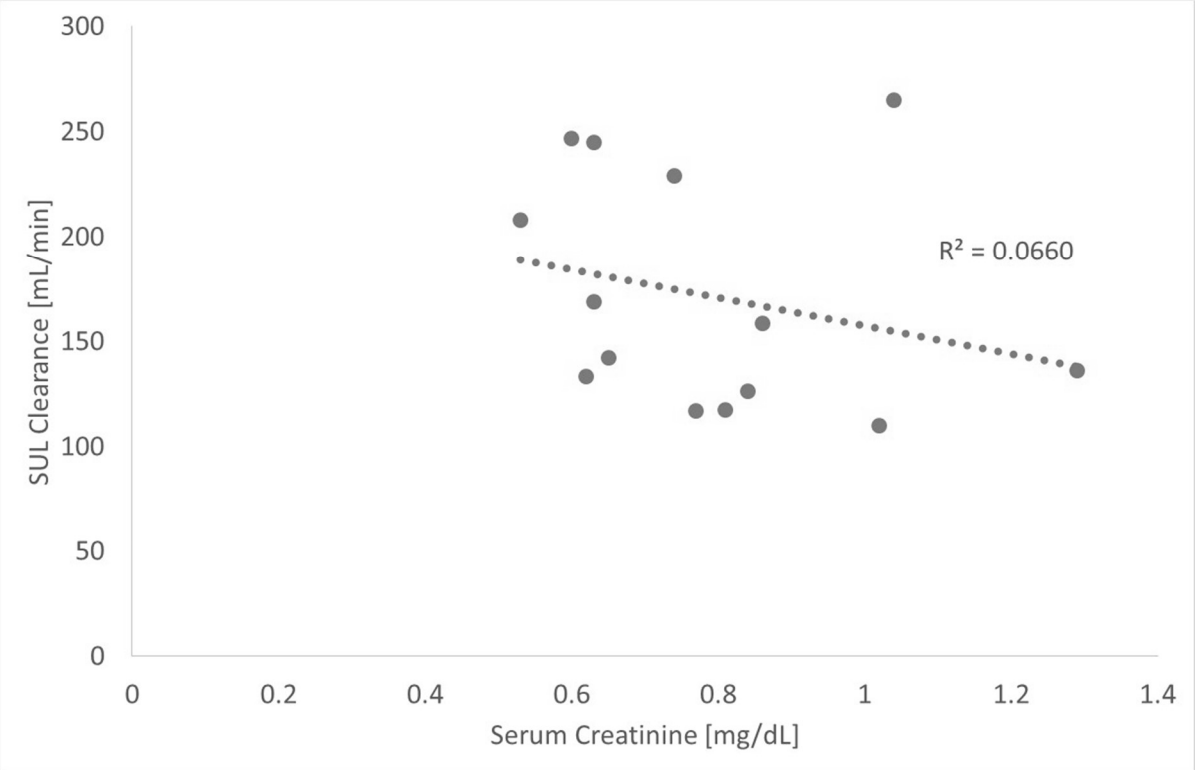


Figure 13-37 Correlation plot of ampicillin volume of distribution and weight.

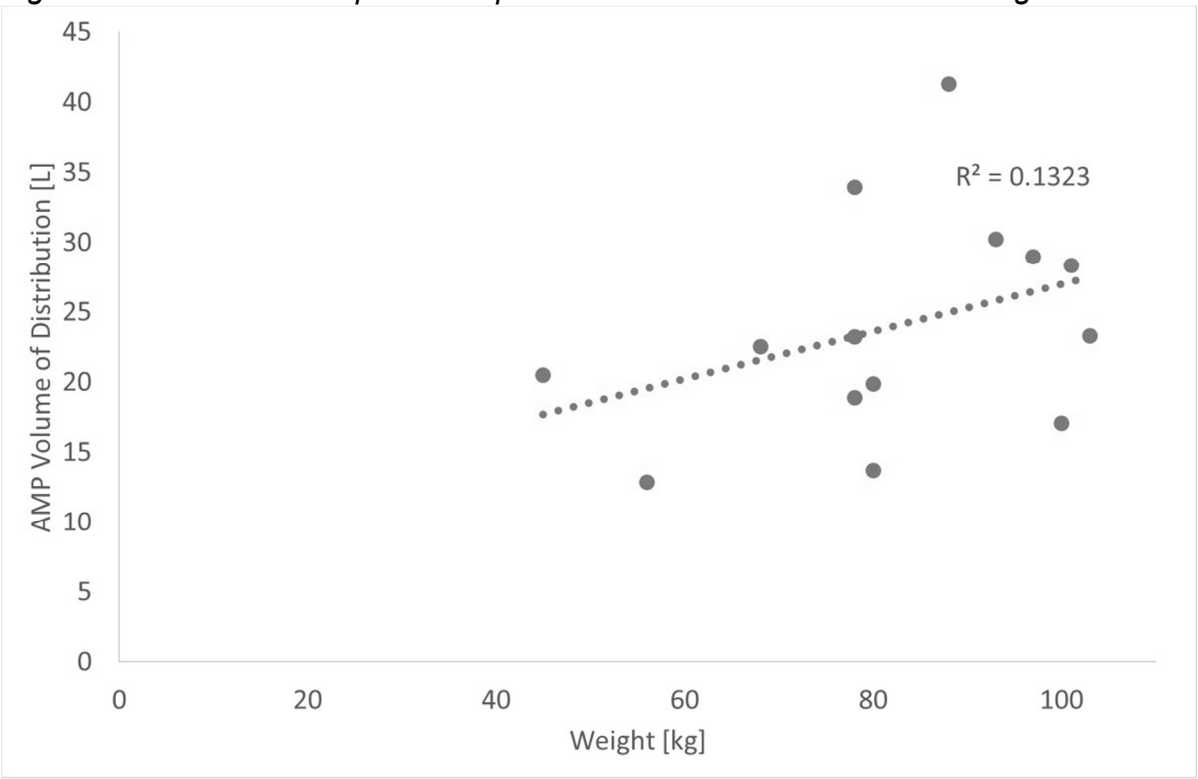


Figure 13-38 Correlation plot of sulbactam volume of distribution and weight.

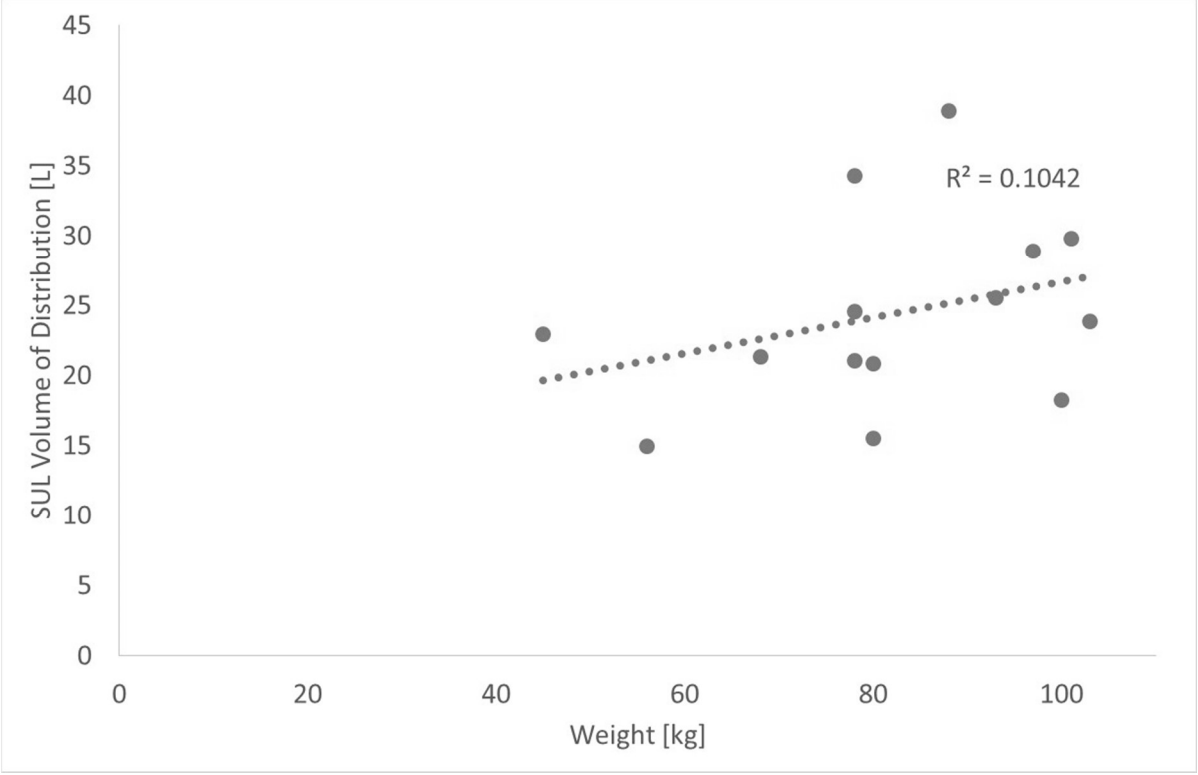


Figure 13-39 Correlation plot of ampicillin volume of distribution and BMI.

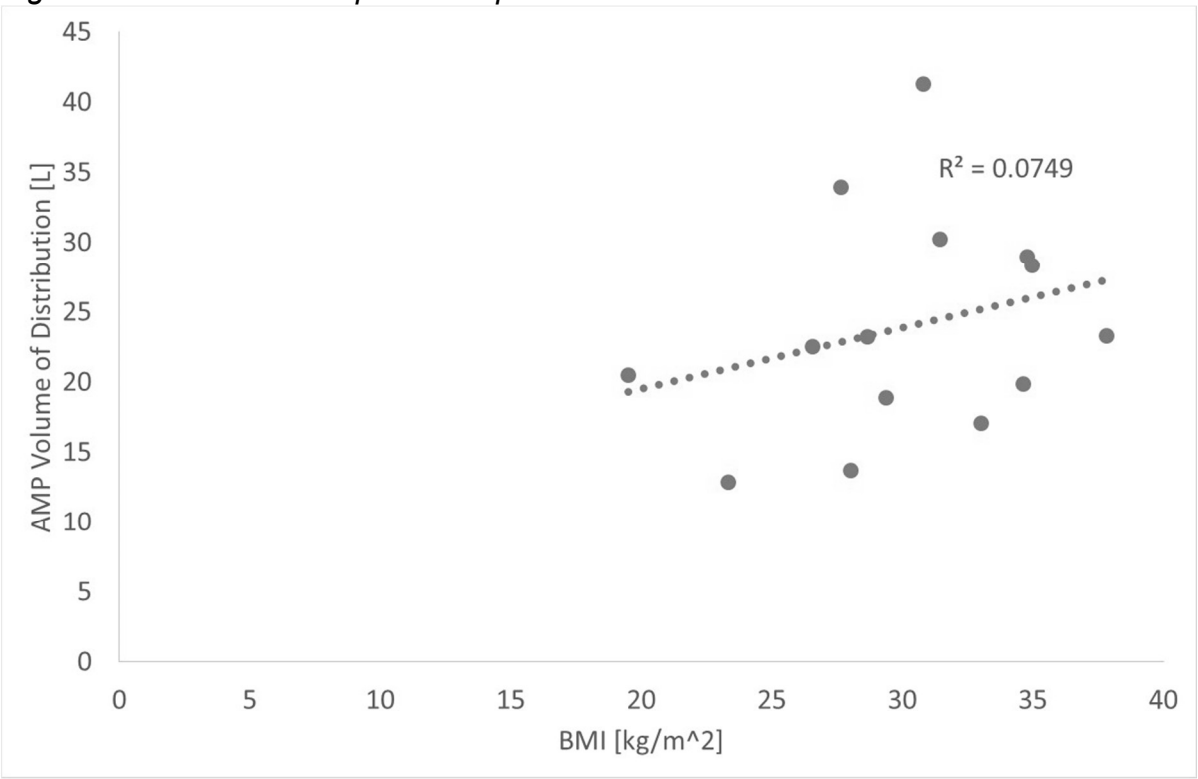


Figure 13-40 Correlation plot of sulbactam volume of distribution and BMI.

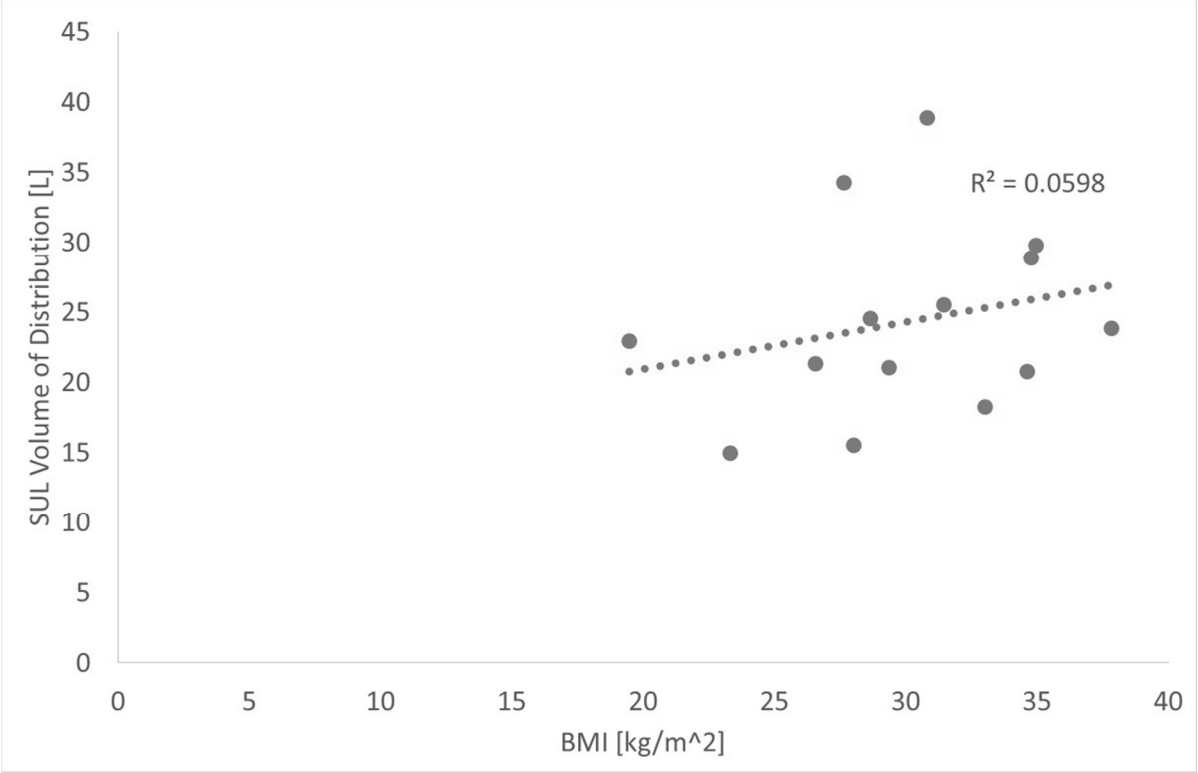


Figure 13-41 Correlation plot of ampicillin volume of distribution and lean body mass.

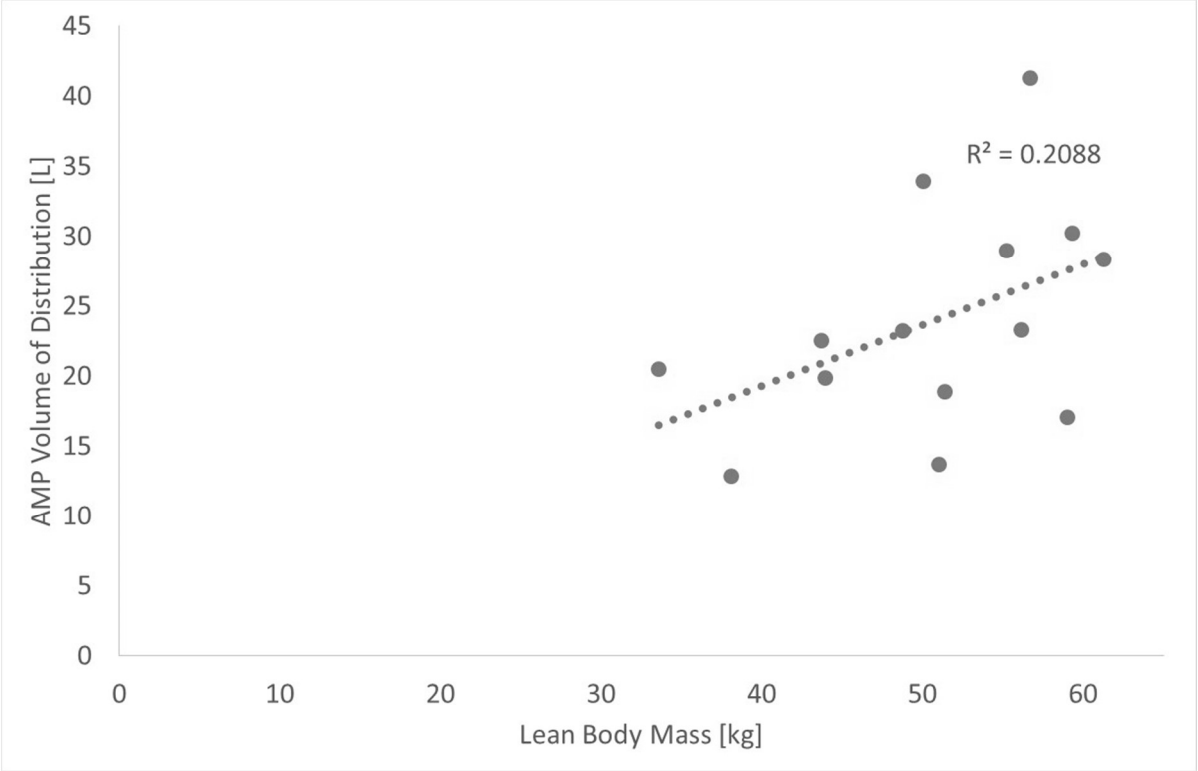


Figure 13-42 Correlation plot of sulbactam volume of distribution and lean body mass.

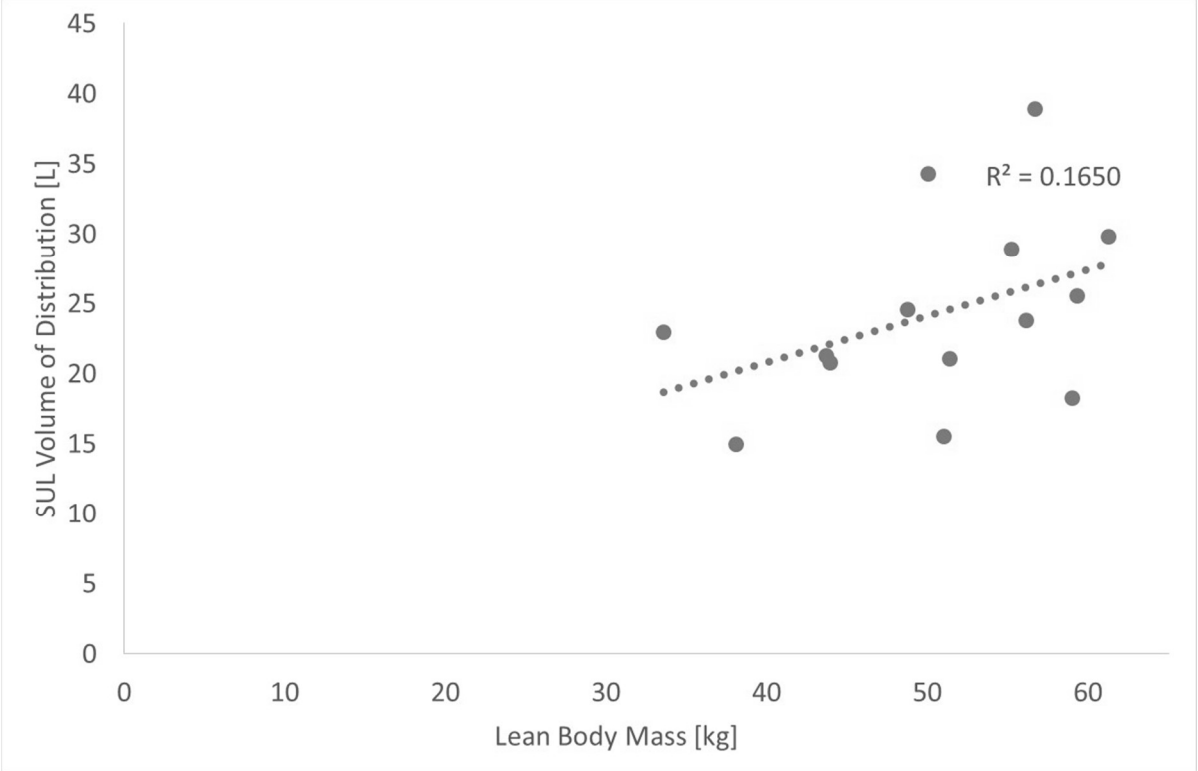


Figure 13-43 Correlation plot of ampicillin volume of distribution and height.

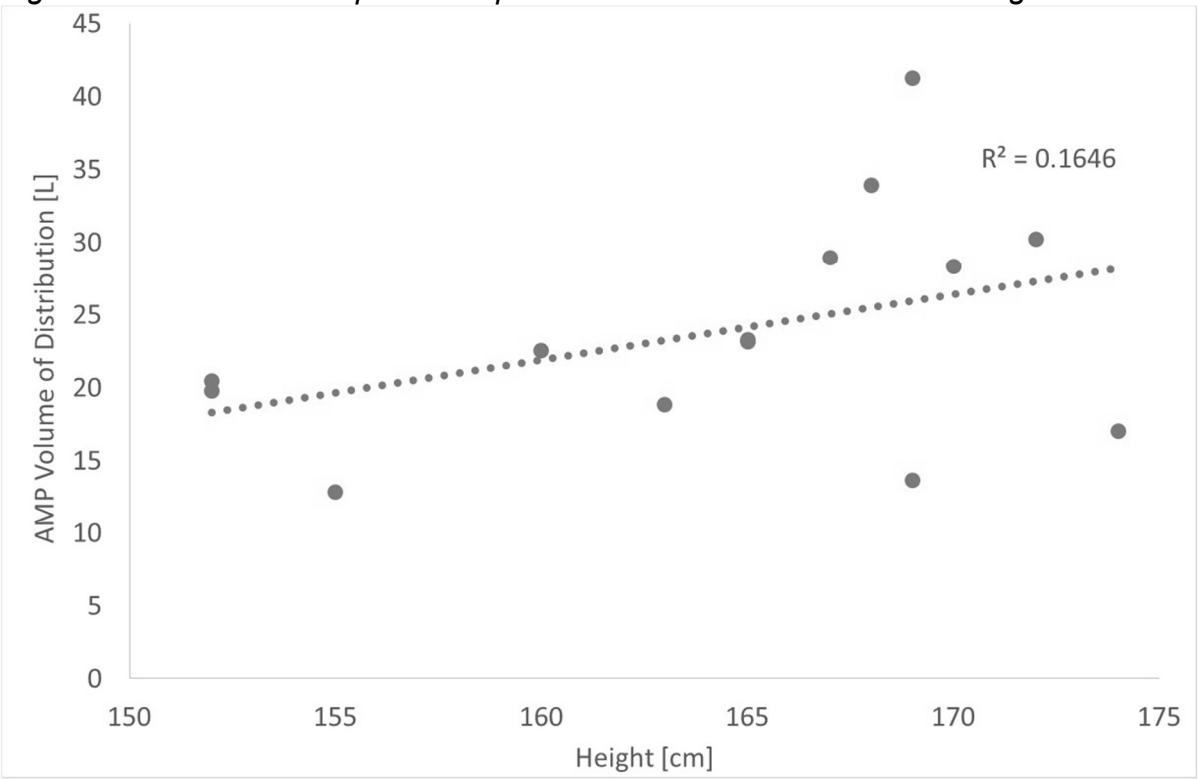
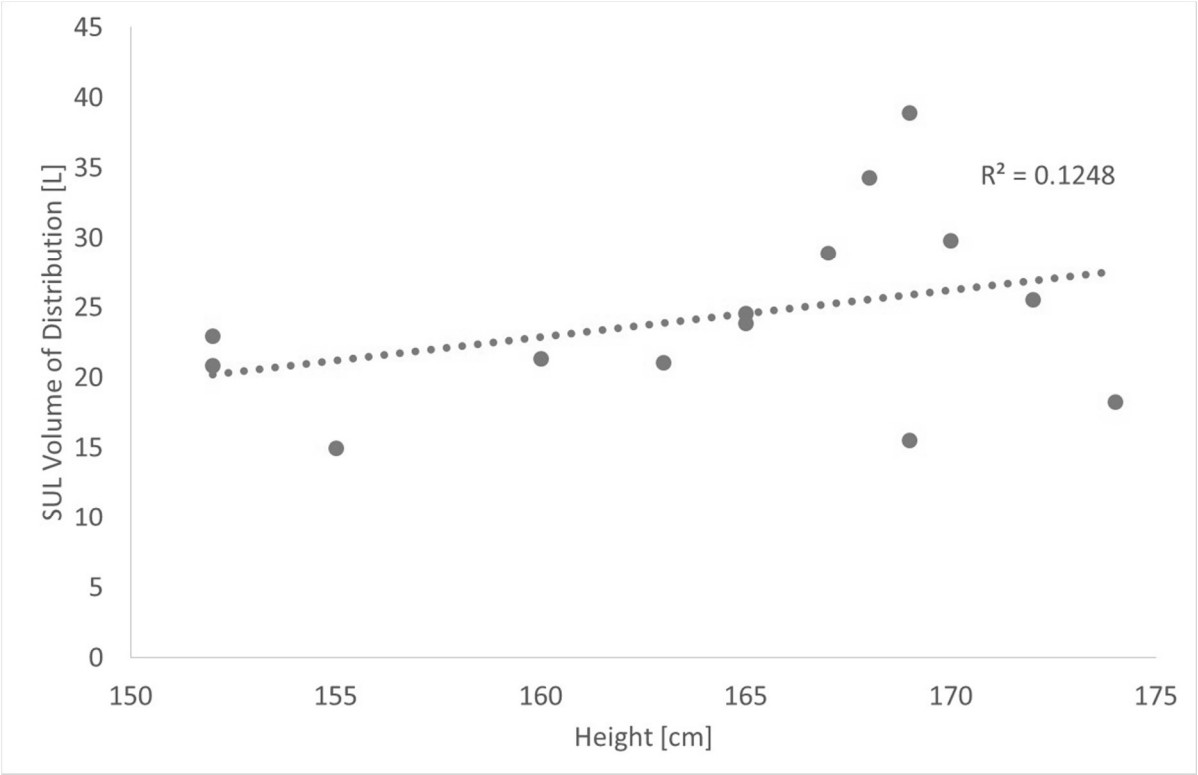


Figure 13-44 Correlation plot of sulbactam volume of distribution and height.



13.2.3. Correlations of ampicillin and sulbactam concentrations and penetration into cortical vs. cancellous bone and vs. time elapsed between the start of infusion and time of bone resection (Δt)

Figure 13-45 Correlation plot of ampicillin concentrations in cortical and cancellous bone.

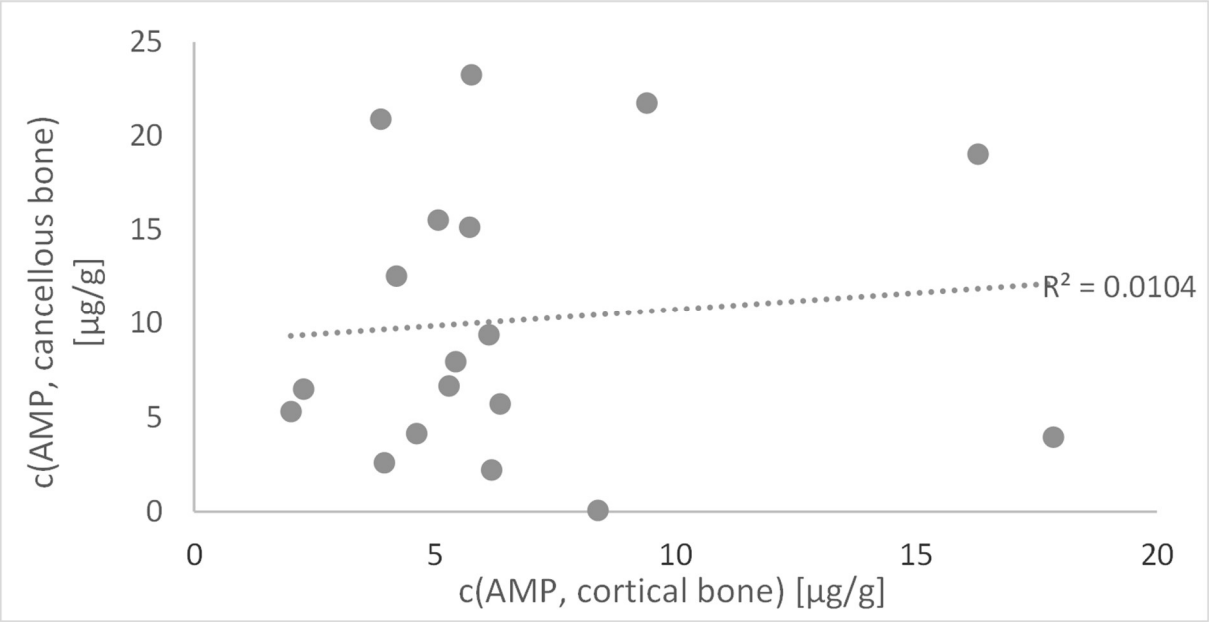


Figure 13-46 Correlation plot of sulbactam concentrations in cortical and cancellous bone.

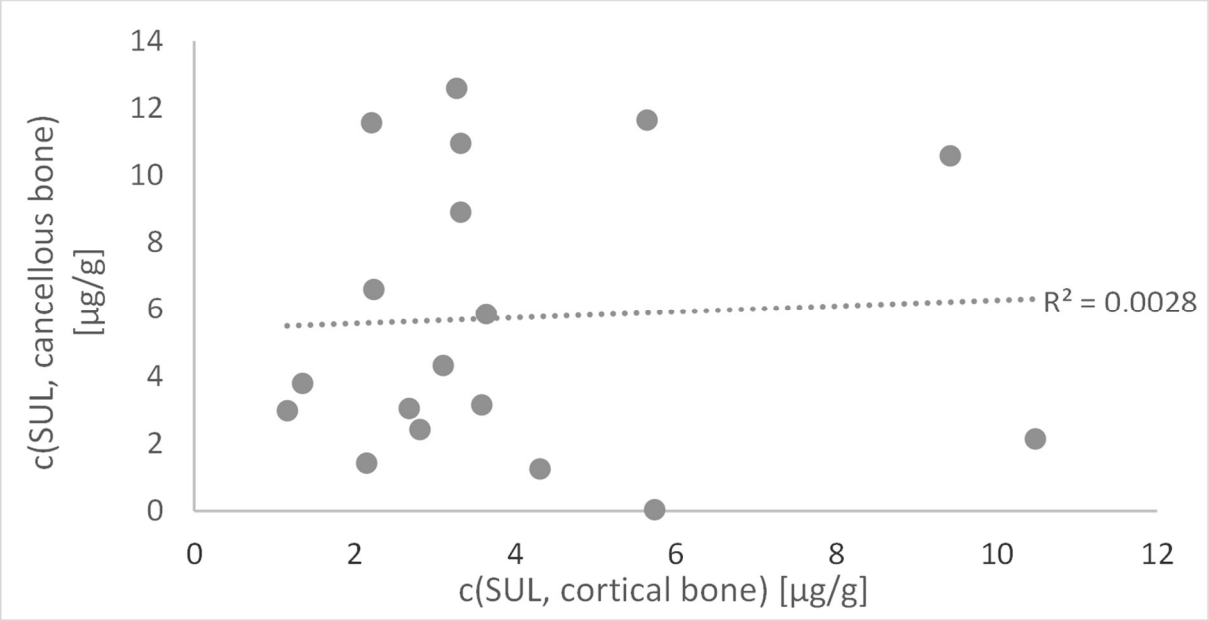


Figure 13-47 Correlation plot of ampicillin penetration into cortical vs. penetration into cancellous bone.

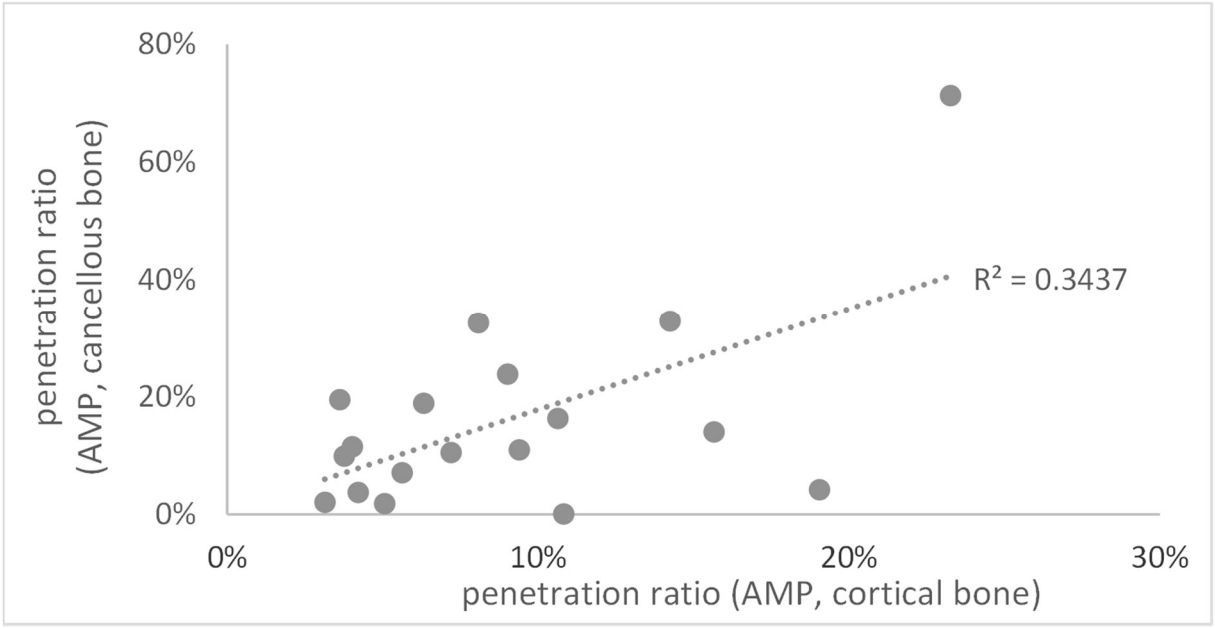


Figure 13-48 Correlation plot of sulbactam penetration into cortical vs. penetration into cancellous bone.

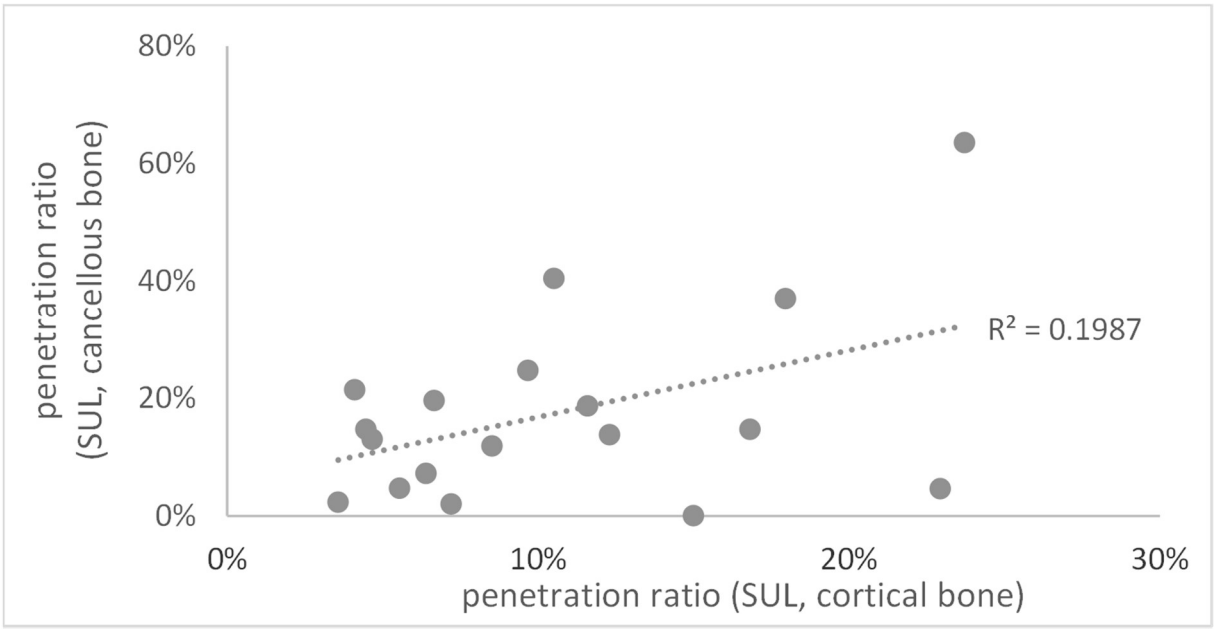


Figure 13-49 Correlation plot of ampicillin concentrations in cortical bone vs. ⊿t.

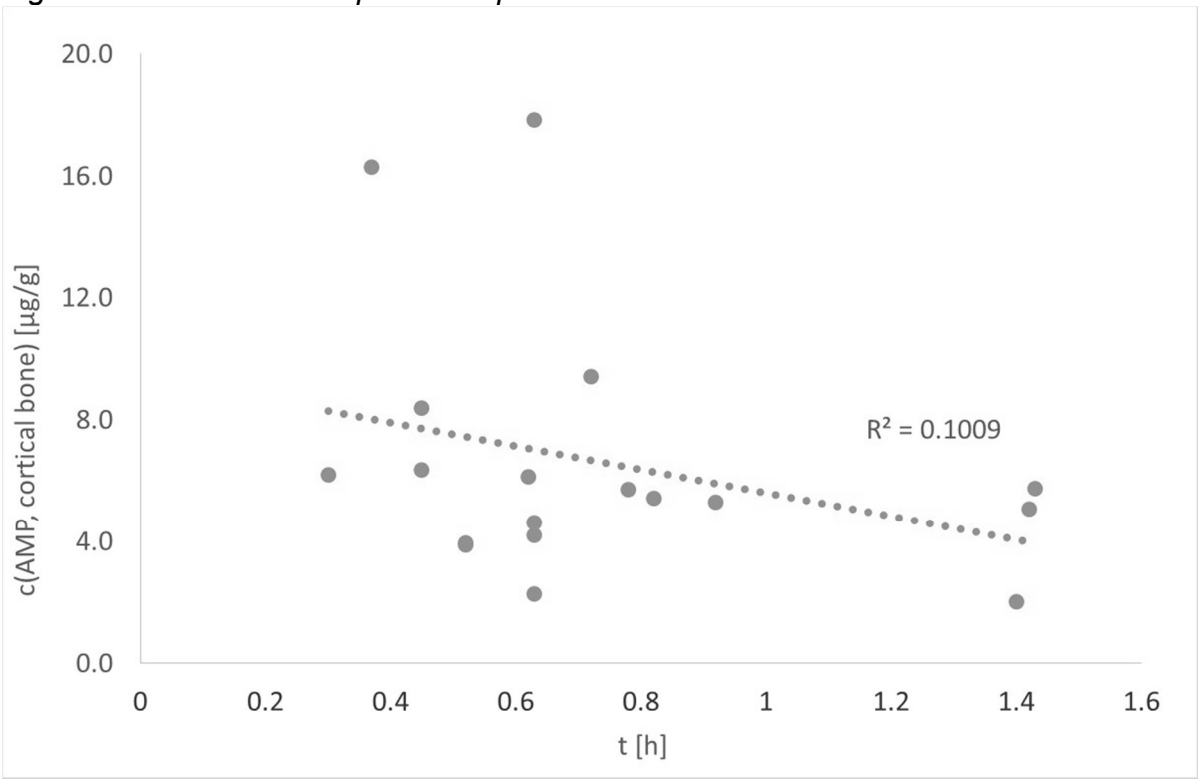


Figure 13-50 Correlation plot of sulbactam concentrations in cortical bone vs. ⊿t.

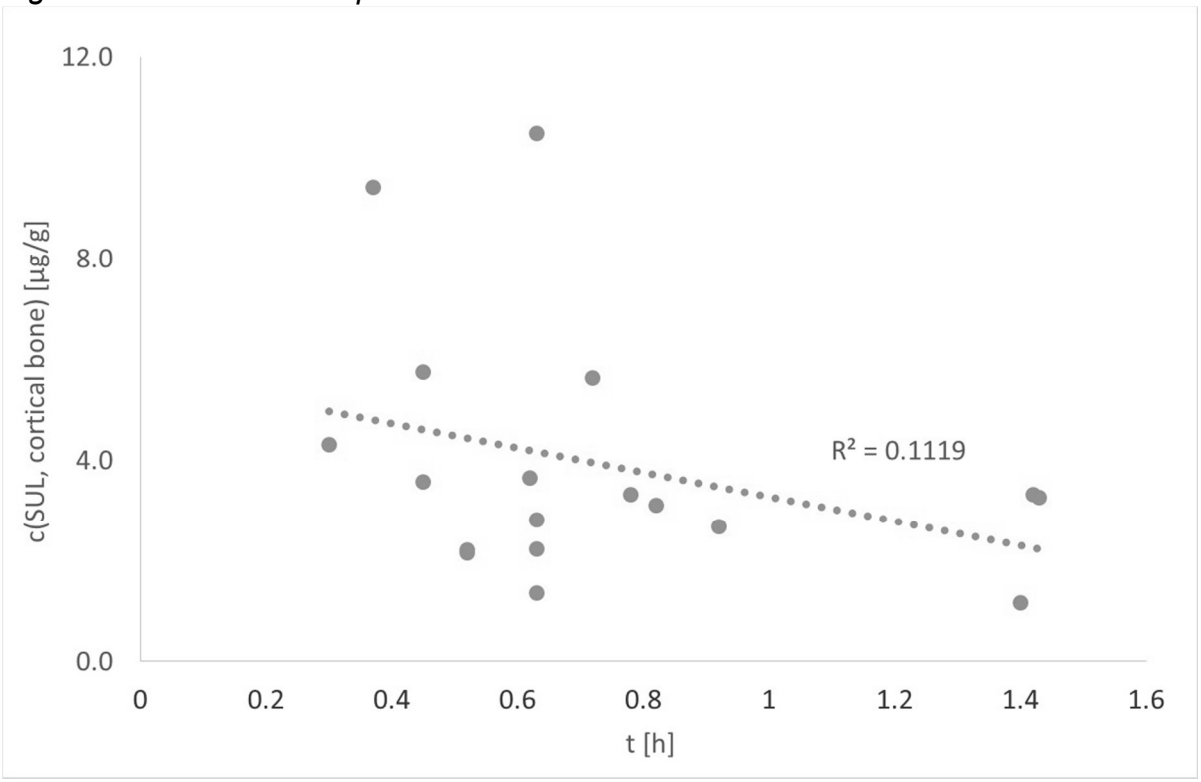


Figure 13-51 Correlation plot of ampicillin concentrations in cancellous bone vs. ⊿t.

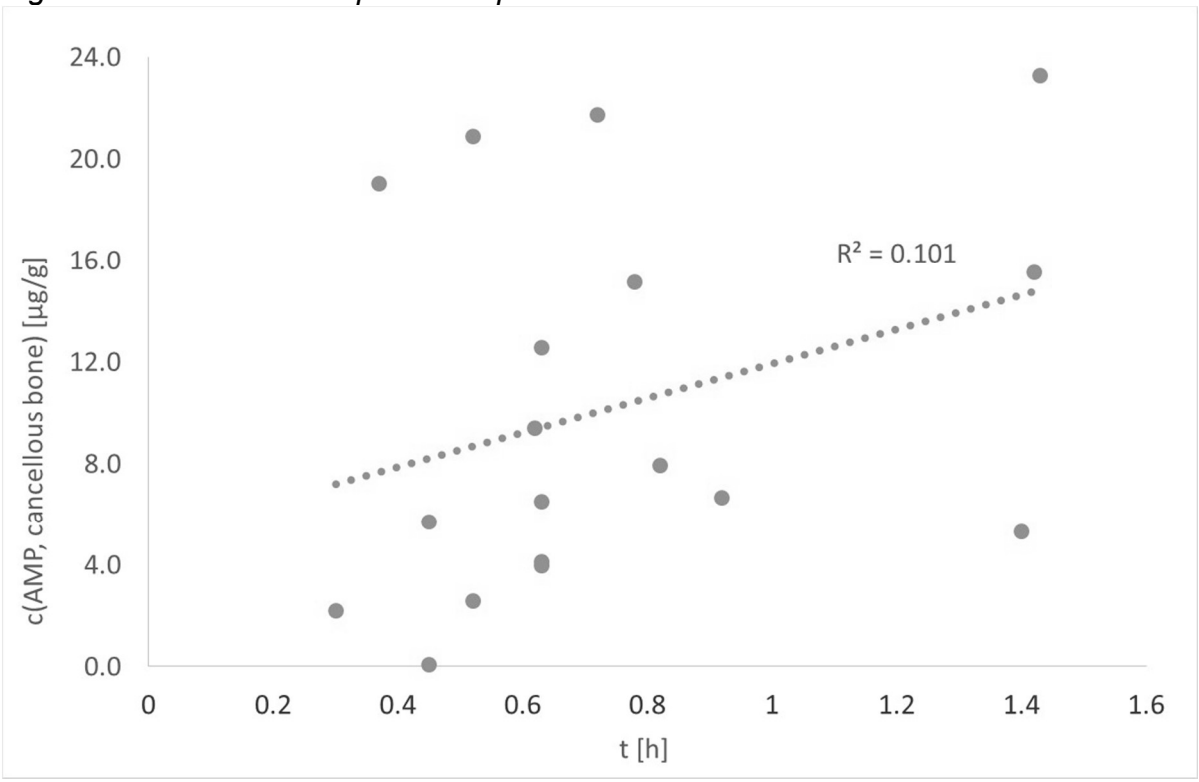


Figure 13-52 Correlation plot of sulbactam concentrations in cancellous bone vs. ⊿t.

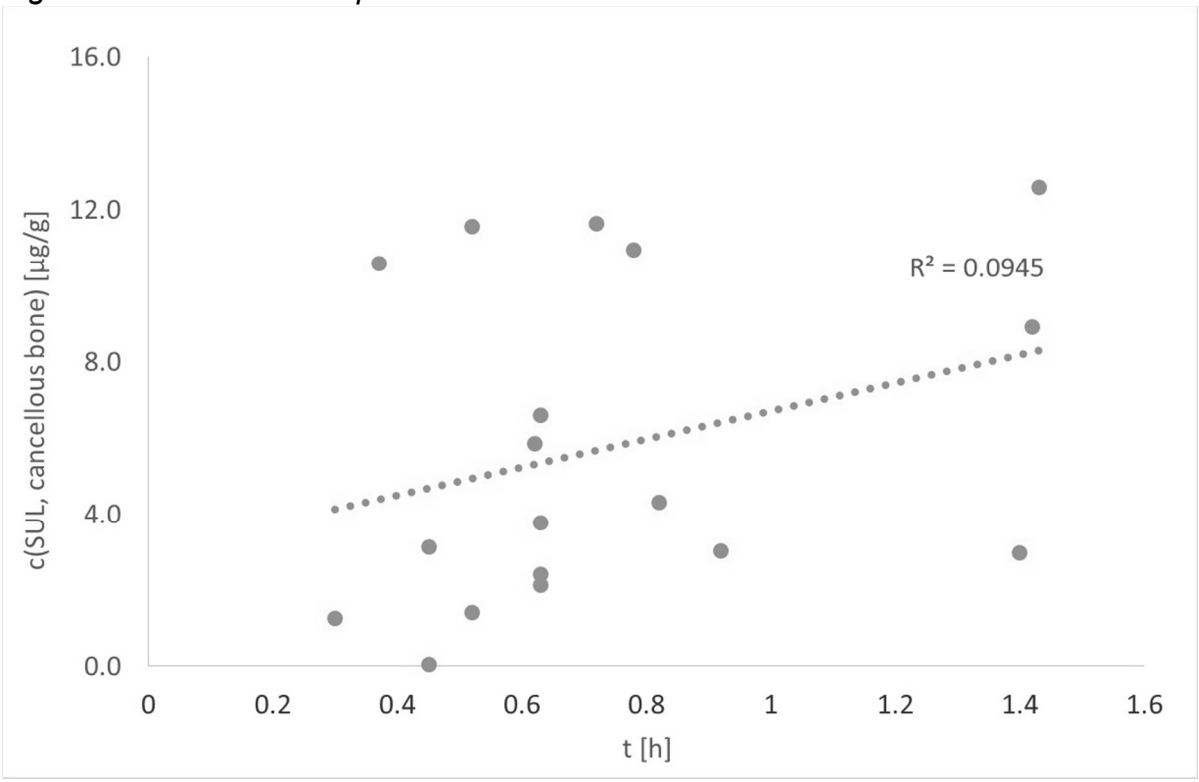


Figure 13-53 Correlation plot of ampicillin penetration into cortical bone vs. Δt.

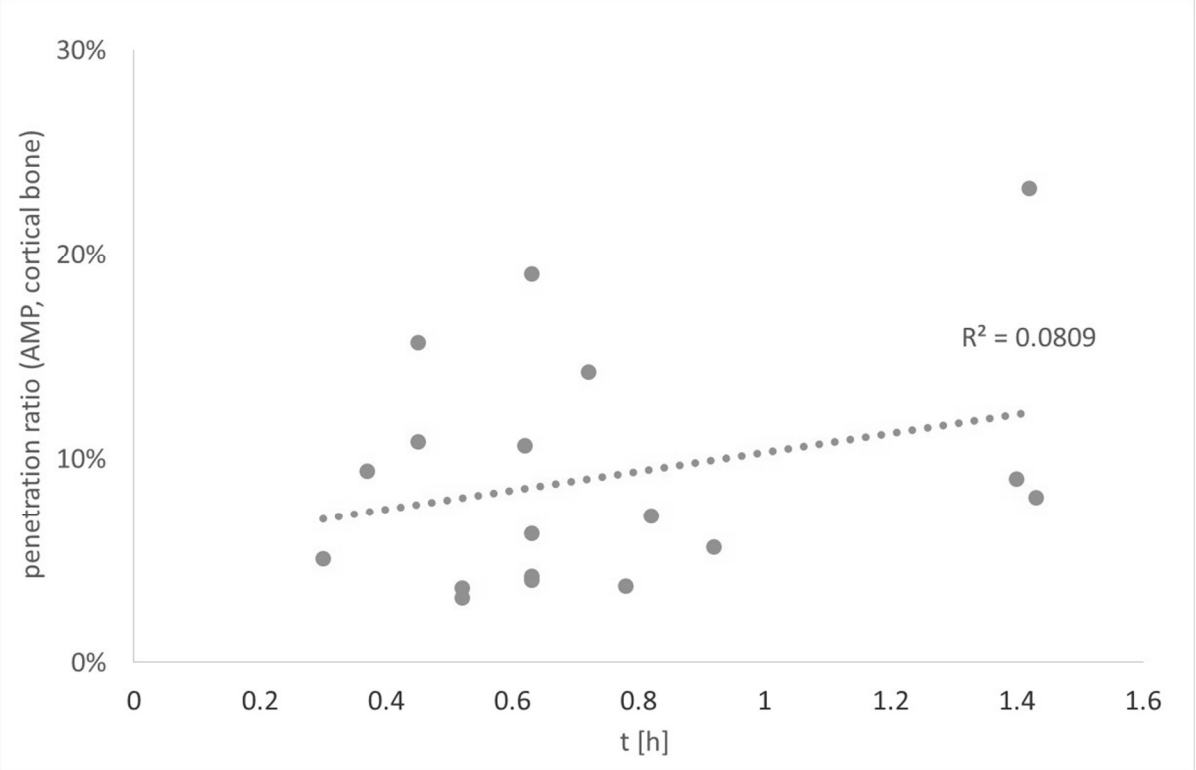


Figure 13-54 Correlation plot of sulbactam penetration into cortical bone vs. Δt.

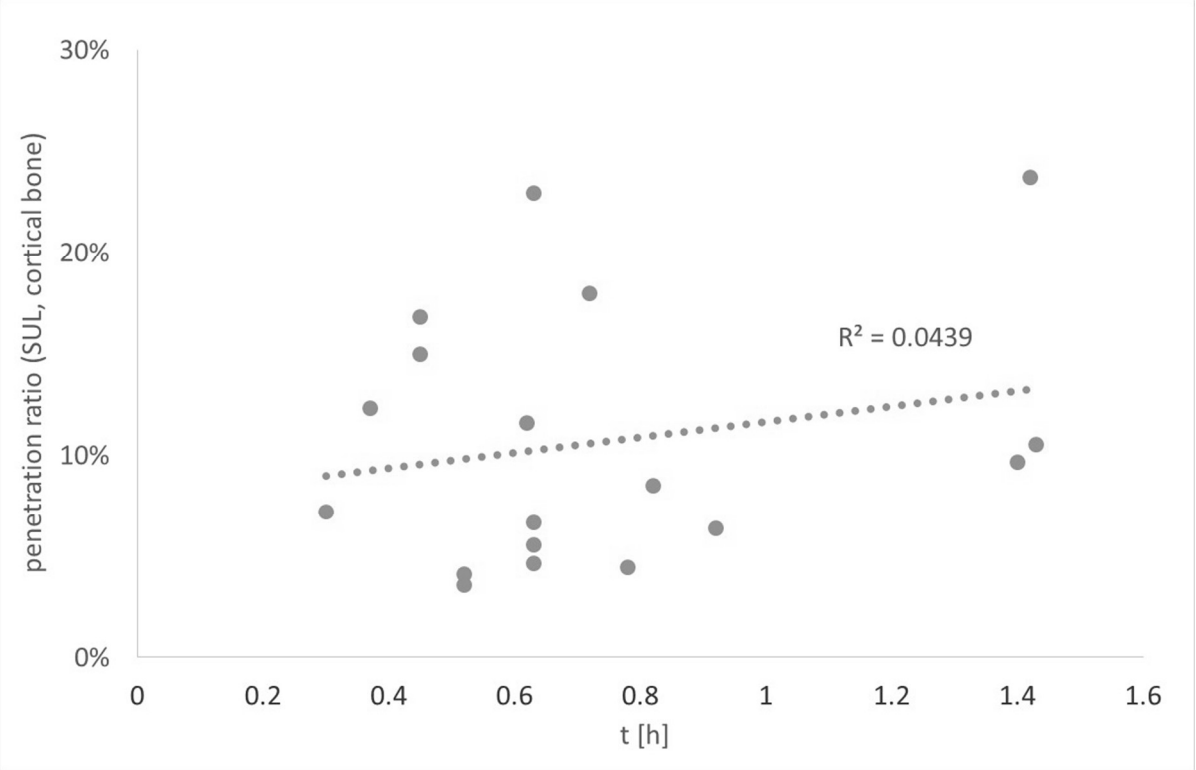


Figure 13-55 Correlation plot of ampicillin penetration into cancellous bone vs. ⊿t.

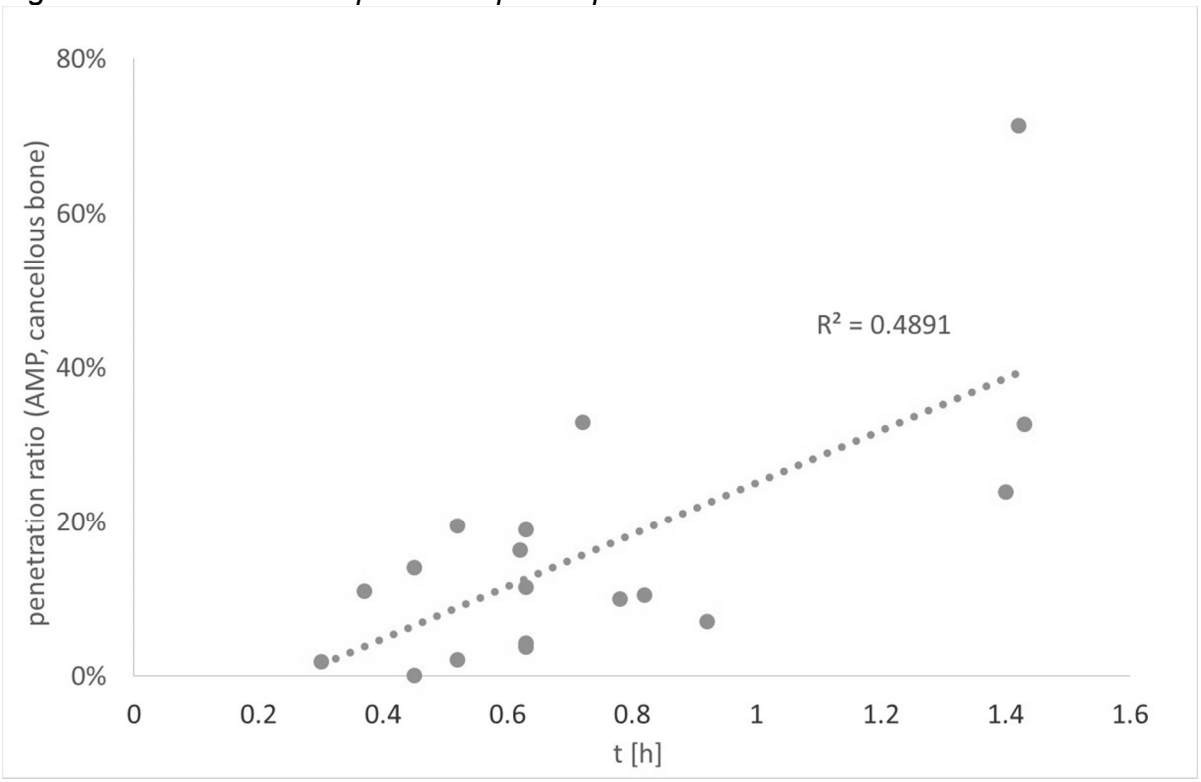
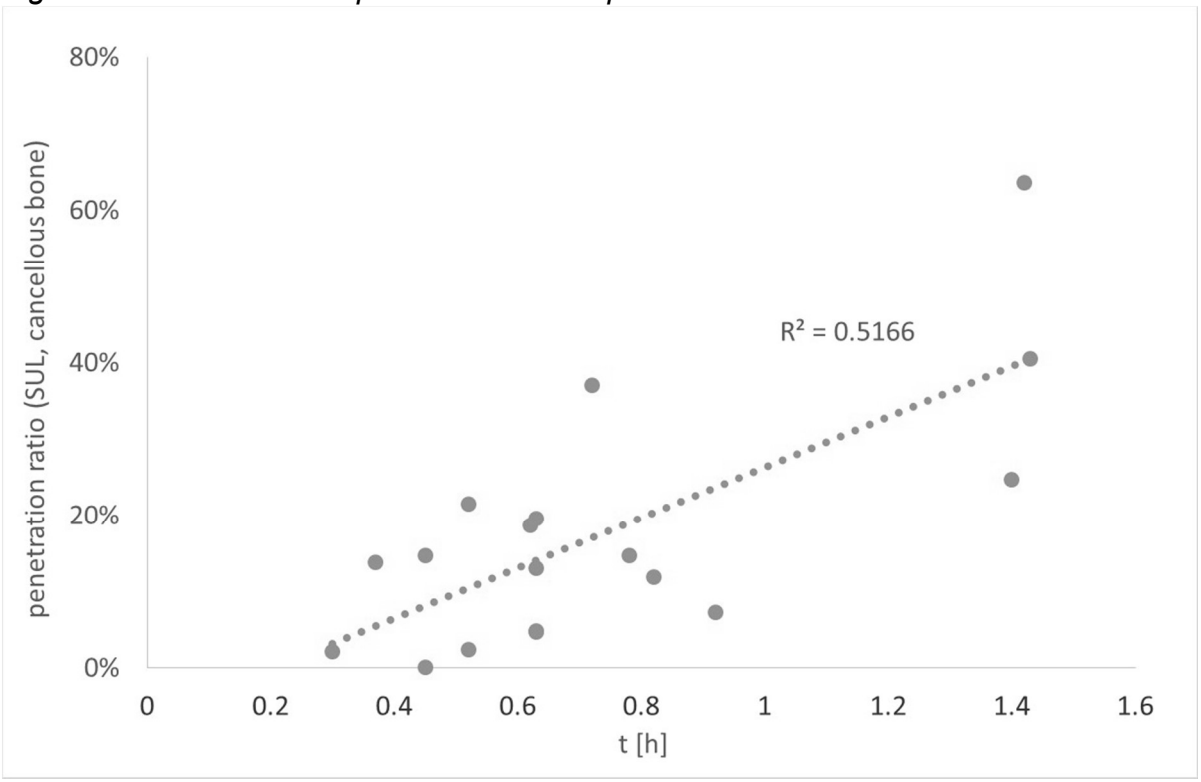


Figure 13-56 Correlation plot of sulbactam penetration into cancellous bone vs. ⊿t.



14. Documentation of Authorship

14.1. Publications reprinted in this thesis

Chapter 7.	**Munz M[A], Pretscher D[B], Wilhelm M[C], Holzgrabe U[D], Sörgel F[E], Birkmann J[F]:** Azathioprine-induced reversible EBV-associated Hodgkin-like lymphoma after immunosuppressive therapy for autoimmune hepatitis. Int J Clin Pharmacol Ther. 2018;56:142-147.

Author	**A**	**B**	**C**	**D**	**E**	**F**
Finding and interpreting clinical data	x	x				x
Literature analysis and interpretation	x					
Manuscript writing	x					x
Correction of manuscript	x	x	x	x	x	x
Corresponding author					x	
Supervision of Martin Munz				x	x	

Chapter 8.	**Munz M[A], Grummich H[B], Birkmann J[C], Wilhelm M[D], Holzgrabe U[E], Sörgel F[F].** Severe Drug-Induced Liver Injury as an Adverse Drug Event of Antibiotics: A Case Report and Review of the Literature. Chemotherapy. 2017;62(6):367-373.

Author	**A**	**B**	**C**	**D**	**E**	**F**
Finding and interpreting clinical data	x	x				
Literature analysis and interpretation	x					
Manuscript writing	x		x			
Correction of manuscript	x		x	x	x	x
Corresponding author						x
Supervision of Martin Munz					x	x

14.2. Unpublished chapters

14.2.1. Overview of pharmacokinetic studies of imipenem / cilastatin and meropenem in critically ill patients and healthy volunteers

The writing of these chapters including all literature searches were performed entirely by the author of this thesis.

14.2.2. Therapeutic drug management and population pharmacokinetics of imipenem / cilastatin and meropenem in critically ill patients

The laboratory team of the Institute for Biomedical and Pharmaceutical Research – IBMP performed the bio-analytical parts of the imipenem / cilastatin and meropenem study described in this thesis. The analytical methods were developed and validated by Christoph Stelzer and Dr. Martina Kinzig. The population PK analysis for imipenem / cilastatin and meropenem was performed by Dr. Jürgen Bulitta. The author contributed to the development of the study protocol, the registration of the study and the clinical and the bio-analytical work related to the imipenem / cilastatin and meropenem study. The author performed the non-compartmental analysis (NCA) of the pharmacokinetic data. The author of this thesis and Dr. Jürgen Bulitta did the writing of these sections.

14.2.3. Bone penetration

The laboratory team of the Institute for Biomedical and Pharmaceutical Research – IBMP performed the bio-analytical parts of the bone penetration study of ampicillin / sulbactam described in this thesis. The analytical methods were developed and validated by Christoph Stelzer and Dr. Martina Kinzig. The author contributed to the development of the blood and bone sampling protocol. In addition, the author contributed to the clinical and the bio-analytical work related to this study. The author of this thesis performed the writing of this section and the NCA of the pharmacokinetic data of ampicillin / sulbactam.

15. Erklärung zu den Eigenanteilen des Doktoranden an Publikationen und Zweitpublikationsrechten bei einer teilkumulativen Dissertation.

Für alle in dieser teilkumulativen Dissertation verwendeten Manuskripte liegen die notwendigen Genehmigungen der Verlage („reprint permission“) für die Zweitpublikation vor, außer das betreffende Kapitel ist noch gar nicht publiziert. Dieser Umstand wird durch die genaue Angabe der Literaturstelle der Erstpublikation auf der ersten Seite des betreffenden Kapitels deutlich gemacht.

Die Mitautoren der in dieser teilkumulativen Dissertation verwendeten Manuskripte sind sowohl über die Nutzung als auch über die oben angegebenen Eigenanteile informiert.

Die Beiträge der Mitautoren an den Publikationen sind in den vorausgehenden Tabellen aufgeführt.

Prof. Dr. Ulrike Holzgrabe

Prof. Dr. Fritz Sörgel

Martin Munz