

Original Article

Pharmacokinetics of ertapenem in critically ill patients with acute renal failure undergoing extended daily dialysis

Olaf Burkhardt^{1,*}, Carsten Hafer^{2,*}, Anita Langhoff², Volkhard Kaever³, Vipul Kumar⁴, Tobias Welte¹, Hermann Haller², Danilo Fliser² and Jan T. Kielstein²

¹Department of Pulmonary Medicine, ²Department of Nephrology, ³Department of Pharmacology and Toxicology, Medical School Hannover, Hannover, Germany and ⁴Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL, USA

Abstract

Background. Extended (daily) dialysis (EDD) is an increasingly popular mode of renal replacement therapy in the ICU (intensive care unit) as it combines the advantages of intermittent haemodialysis (IHD) and continuous renal replacement therapy (CRRT), i.e. excellent detoxification accompanied by cardiovascular tolerability. The aim of this study was to evaluate pharmacokinetics (PK) of ertapenem, the newest carbapenem with once-daily dosing, in critically ill patients with anuric acute renal failure (ARF) undergoing EDD.

Patients and Methods. In a single-centre, prospective, open-label study six ICU patients with ARF undergoing EDD were treated with 1 g ertapenem given as a single intravenous dose. EDD was performed using a high-flux dialyzer (polysulphone, 1.3 m²). Blood and dialysate flow were 160 mL/min, and the length of treatment was 480 min. Plasma samples were collected at different time-points up to 24 h after medication. Drug concentrations were determined by a validated LC-MS method. Free drug concentrations were estimated using a two-class binding site equation.

Results. After a single dose of 1000 mg free ertapenem, protein-unbound plasma concentrations exceeded a MIC₉₀ value of 2 mg/L for >20 h after dosing. The clearance of the tested dialyzer was 38.5 ± 14.2 mL/min.

Conclusions. In contrast to patients undergoing regular IHD, in which a dose reduction is required, our data suggest that in patients treated with EDD a standard dose of ertapenem (1 g/day), i.e. dose for patients without renal failure, is required to maintain adequate plasma drug levels.

Keywords: ertapenem; ICU patients; pharmacokinetics; renal insufficiency; renal replacement therapy

Introduction

Ertapenem, a parenteral 1-β-methyl-carbapenem with *in vitro* activity against many common aerobic and anaerobic gram-positive and gram-negative bacteria, was licensed in the USA in November 2001 and in Europe in April 2002 for several indications, such as complicated intra-abdominal infections, complicated skin and skin-structure infections, acute pelvic infections, complicated urinary tract infections and community-acquired pneumonia [1]. Additionally, in August 2006, ertapenem has been approved by both the FDA and EMEA for the prophylaxis of surgical site infection following elective colorectal surgery in adult patients [1]. The substance was selected for clinical development partially based on its pharmacokinetics (PK) [1]. Due to a plasma elimination half-life of ~4 h in healthy young adults, which reflects a high plasma protein binding (90–95%), administration of 1 g ertapenem once a day is recommended [1–3]. Approximately 80% of an intravenous dose of ertapenem is excreted in urine either as unchanged drug or as ring-opened metabolite in nearly equal amounts. Hence, in patients with renal insufficiency AUC_{0-∞} values of ertapenem increased with decreasing renal function with mean increases of 7% in mild (CL_{CR} 79 mL/min/1.73 m²), 53% in moderate (CL_{CR} 40 mL/min/1.73 m²), 158% in advanced (CL_{CR} 17 mL/min/1.73 m²) and 192% in end-stage renal disease requiring haemodialysis [4]. The terminal elimination half-life of ertapenem reported by Mistry *et al.* was 4.4 h in mild renal insufficiency, 6.1 h in moderate, 10.6 h in advanced and 14.1 h in outpatients with end-stage renal disease [4]. Intermittent haemodialysis (IHD) cleared ~30% of ertapenem, which has a molecular weight of 497.5 Da. Based on results of this study, the recommended dose for patients with mild and moderate renal insufficiency is unchanged at 1 g once a day and for patients with advanced (CL_{CR} ≤30 mL/min/1.73 m²) and end-stage renal disease is reduced to 0.5 g once a day [1]. If the daily dose is given within 6 h prior to a dialysis session, a supplementary dose of 30% of the daily dose is recommended post-dialysis. However, in intensive care patients suffering from sepsis and multiple organ failure,

Correspondence and offprint requests to: Jan T. Kielstein, Department of Nephrology, Medical School Hannover, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany. Tel: +49-511-532-6319; Fax: +49-511-532-4005; E-mail: Kielstein@yahoo.com

*The authors have contributed equally to this work.

PK of commonly used antibiotics can be significantly altered [5]. Extended daily dialysis (EDD) is an increasingly popular mode of renal replacement therapy in intensive care units (ICUs) throughout the world [6]. EDD removes drugs such as levofloxacin, meropenem, vancomycin and linezolid more efficiently compared with standard IHD three times a week or continuous modes of renal replacement therapy [7–10]. As there are no data on ertapenem in critically ill patients undergoing renal replacement therapy, we determined single-dose ertapenem PK in critically ill patients with septic shock and anuric acute renal failure (ARF) undergoing EDD.

Patients and methods

Study design and subjects

The Hannover Medical School Ethics Committee approved the study protocol. Adult intensive care patients with anuric ARF being treated with EDD and receiving ertapenem were enrolled. The choice of the antibiotic for each patient was made on clinical grounds. Patients were entered into the study after informed consent had been obtained from the patient or the patient's legal representative. All patients received 1 g intravenous ertapenem (Invanz[®], MSD SHARP & DOHME, Haar, Germany) over 30 min, irrespective of their body weight, age and sex.

EDD was performed in all patients using the 75 l GENIUS[®] batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany) with a polysulphone high-flux dialyzer (F60S, surface area 1.3 m², Fresenius Medical Care, Bad Homburg, Germany) as previously described [11]. The technical details of the system are explained elsewhere [12]. The average dialysis time during the study was 480 ± 0 min, and mean blood and counter current dialysate flow was 160 ± 0 mL/min. Vascular access in all patients was achieved by a double lumen catheter inserted in either the internal jugular or the femoral vein. Blood samples were drawn from the arterial line placed in the radial or femoral artery.

Ertapenem sampling and analysis

Blood samples (5 mL) were collected via an arterial catheter, before ertapenem infusion and 0.5, 1, 2, 4, 6, 8 h after the end of the ertapenem infusion. Furthermore, samples were drawn 2, 4, 6 and 8 h after the start of EDD. Additional blood samples were drawn pre- and post-dialysis in order to calculate the dialyzer clearance from the arteriovenous concentration difference and blood flow. To study post-EDD pharmacokinetics, samples were drawn 0.5, 1, 3 and 8 h after the end of EDD. All samples were centrifuged at 1300 g for 10 min at 4°C. Plasma was separated and stored at –80°C until analysis.

Concentrations of ertapenem in plasma were determined by validated SPE-liquid chromatography–mass spectrometry methods (LC-MS) as previously described [13]. All calibration functions were linear within the relevant assay ranges. The lower limit of quantification in plasma was 0.1 µg/mL. Variability in intra- and inter-day precision

(CV) and accuracies (RE) were <10%. Recoveries were >90%.

Pharmacokinetic analysis

Noncompartmental pharmacokinetic analysis for the data was performed using the WinNonlin software program (WinNonlin version 3.1, Pharsight Corporation, Mountain View, CA, USA). The maximum concentration in plasma (C_{max}) and time to reach C_{max} (T_{max}) after drug administration were obtained directly by visual examination of concentration–time data. The area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$) was calculated by the log-linear trapezoidal rule until the time of the last quantifiable plasma concentration and then extrapolated to infinity by using the quotient of the last measurable concentration (C_{last}) to the terminal-phase rate constant (β). The terminal elimination rate constant (β) was estimated from the slope of the terminal exponential phase of the logarithmic plasma concentration–time profile using at least three data points. The elimination half-life ($T_{1/2}$) was determined as $0.693/\beta$. The mean residence time (MRT) was calculated as $AUMC_{0-\infty}/AUC_{0-\infty}$, where $AUMC_{0-\infty}$ is the area under the first moment of the concentration–time curve. Total body clearance (Cl_{off}) was determined as $dose/AUC_{0-\infty}$. The apparent volume of distribution during the terminal phase (V_z) was calculated as $dose/(AUC_{0-\infty} \times \beta)$. All data are presented as geometric means ± standard deviations, with the exception of T_{max} , for which median and minimum–maximum ranges are given. The dialysis clearance (CL_{dial}) was estimated from concentrations before (C_{in}) and directly after (C_{out}) the dialysis membrane 10 min after the beginning of the EDD with constant blood and dialysate flow rates.

Estimation of free drug concentration

The free concentrations of ertapenem (C_f) were estimated using a two-class binding site model, which assumes one specific and one non-specific-binding site. This model has been reported to explain well the relation between free and total concentrations of ertapenem in preclinical situations.

$$C_b = \frac{n_1 p_1 k_1 C_f}{1 + k_1 C_f} + n_2 p_2 k_2 C_f,$$

where C_b represents the bound concentration and C_f is the free ertapenem concentration, n_1 and n_2 represent the number of binding sites and p_1 and p_2 are concentrations of albumin (specific) and remaining plasma proteins (non-specific), respectively. k_1 and k_2 are the association rate constants for the specific and non-specific binding sites. The free, bound and total (C_t) drug concentrations are related as

$$C_t = C_f + C_b.$$

The literature data were fitted using the Scientist software (Scientist version 2.0, Micromath Inc., Saint Louis, MO, USA). The binding equation was solved for C_f and was used to determine the free ertapenem concentration when

Table 1. Demographic data

Patient	Gender	Age	Height cm	Weight kg	Ultrafiltration ml	Clinical condition
1	F	48	164	68	1600	Oesophageal perforation
2	M	74	168	70	1900	Peritonitis, appendicitis
3	M	76	176	78	2400	Gastric cancer
4	M	49	171	63	3100	Livercirrhosis, oesophageal bleed
5	M	47	175	69	2400	Liver Tx
6	M	62	172	75	3200	Liver Tx, hepatitis C

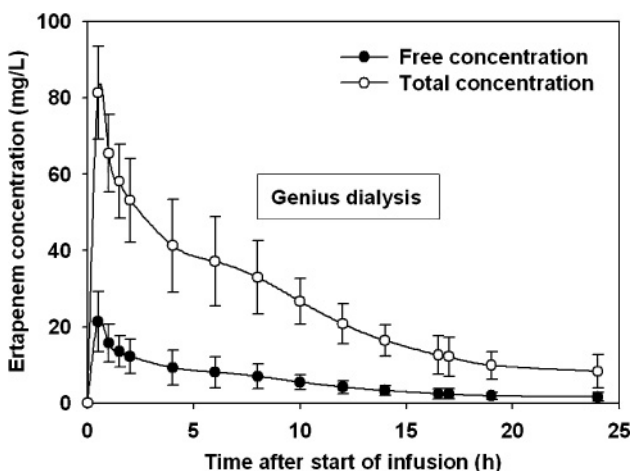


Fig. 1. Time courses of total and free, protein-unbound ertapenem plasma concentrations after administration of a single 1 g intravenous dose in ICU patients with acute renal failure undergoing extended daily dialysis. Infusion period 30 min. Values are geometric means \pm SD, $n = 6$.

C_t and protein concentrations (both total protein and albumin) were available using Microsoft Excel (Excel, Microsoft Corporation, Redmond, WA, USA).

Results

Patient characteristics

We treated six patients with ertapenem. The patient demographic and clinical information is given in Table 1. There were no adverse effects attributable to the use of ertapenem in our patients.

Pharmacokinetic analysis

Pharmacokinetic investigations were completed for all six patients. Mean total and free, protein-unbound ertapenem concentrations for 24-h period are shown in Figure 1, and the time courses of mean free, protein-unbound ertapenem plasma concentrations in relation to MICs of most frequent community-acquired pathogens are shown in Figure 2. The PK parameters as determined using noncompartment analysis are listed in Table 2. For comparison, single-dose PK parameters of ertapenem reported earlier by Burkhardt *et al.*

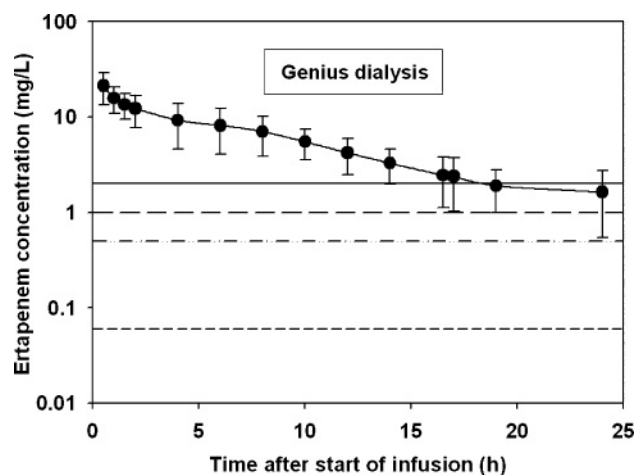


Fig. 2. Time courses of mean free, protein-unbound ertapenem plasma concentrations after administration of a single 1 g intravenous dose in ICU patients with acute renal failure undergoing extended daily dialysis. Horizontal lines indicate MIC₉₀ values for penicillin-resistant *Streptococcus pneumoniae* (MIC₉₀ \leq 2.0 mg/L; ---) most anaerobe bacteria (MIC₉₀ \leq 1.0 mg/L; - - -), methicillin-susceptible *Staphylococcus aureus* and extended-spectrum β -lactamase (ESBL)-producing *Klebsiella pneumoniae* (MIC₉₀ \leq 0.5 mg/L; - · - ·) and non-ESBL-producing Enterobacteriaceae (MIC₉₀ \leq 0.06 mg/L).

in ICU patients with normal renal function and healthy volunteers are also given [14,15]. In our study, we observed that patients with ARF undergoing EDD yielded higher AUC_{0-inf} plasma values than ICU patients with normal renal function and young healthy volunteers. Furthermore, the terminal elimination half-lives of ertapenem in our patients off dialysis were significantly higher in comparison to the other populations ($T_{1/2\text{off}}$ 18.9 versus 4.1 versus 3.8 h). This also holds true for the terminal elimination half-life on EDD ($T_{1/2\text{on}}$) that was 6.7 h. While the total clearance off dialysis in our patients was lower as compared with the values for other patients not requiring renal replacement therapy (Cl_{off} 19.3 versus 43.2 versus 48 mL/min), the total clearance on dialysis (Cl_{dial} 49.5 mL/min) was comparable to controls with normal renal function (48 mL/min) and to ICU patients with impaired renal function not requiring renal replacement therapy (43.2 mL/min). There were no differences in volumes of distribution (V_z 15.9 versus 17.3 versus 15.5 L).

Discussion

This study provides the first pharmacokinetic data of ertapenem in critically ill patients with ARF undergoing EDD.

The incidence of ARF has increased dramatically over the last 25 years. The age-adjusted rate per 10 000 population of hospitalization for ARF increased from 1.8 in 1980 to 36.5 in 2005 (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5712a1.htm>). Since ARF in the ICU is frequently part of a multiple-organ dysfunction syndrome encountered in patients with sepsis [16], we assessed the single-dose pharmacokinetics (PK) of ertapenem, a drug approved for several life-threatening indications such as intra-abdominal infections, skin and

Table 2. Comparison of ertapenem pharmacokinetic data obtained in critically ill patients with acute renal failure (ARF) undergoing extended daily dialysis with data of patients with end-stage renal disease (ESRD) requiring haemodialysis [4], data of critically ill patients with CrClr > 30 ml/min [15] and data of healthy young volunteers [14] previously reported in the literature

Parameter	ICU patients with ARF and EDD (<i>n</i> = 6)	Patients with ESRD requiring haemodialysis [4] (<i>n</i> = 7)	ICU patients (CrClr > 30 mL/min) [15] (<i>n</i> = 17)	Healthy volunteers [14] (<i>n</i> = 6)
C_{max} (mg/L)	81.3 ± 12.1	138.9	90.5 ± 26.1	103.3 ± 26.3
AUC _{0-inf} (mg h/L)	687.4 ± 212.0	1941.5	418.5 ± 171.6	359.7 ± 66.5
T_{max} (h)	0.5 (0.5)	0.5	0.5 (0.5–1.0)	0.5 (0.5)
$T_{1/2off}$ (h)	18.9 ± 5.4	14.1	4.1 ± 1.3	3.8 ± 0.6
$T_{1/2on}$ (h)	6.7 ± 0.4	NA	NA	NA
MRT (L)	10.7 ± 1.6	NA	5.7 ± 1.7	4.6 ± 0.9
V_z (L)	15.9 ± 3.2	NA	17.3 ± 5.9	15.5 ± 3.4
CL _{off} (mL/min)	19.3 ± 11.4	NA	43.2 ± 23.7	48.0 ± 8.5
CL _{dial} (mL/min)	49.5 ± 10.9	NA	NA	NA

C_{max} : peak plasma concentration; AUC: area under the curve; T_{max} : time of maximal plasma concentration; $T_{1/2off}$: half-life off dialysis treatment; $T_{1/2on}$: half-life on dialysis treatment; MRT: mean residence time; V_z : volume of distribution; CL_{off}: drug clearance off extended dialysis; CL_{dial}: dialysis clearance; NA: not available; ICU: intensive care unit.

skin-structure infections, acute pelvic infections, complicated urinary tract infections and pneumonia, community-acquired and ‘early-onset’ nosocomial infections, especially as PK data in this patient group are non-existent.

Why cannot we use PK data from ESRD patients undergoing IHD in an outpatient setting?

Firstly, septic patients behave differently than stable outpatients. Like other antimicrobial agents, most information about PK of ertapenem was obtained from studies in healthy volunteers. However, recent results from pharmacokinetic/pharmacodynamic (PK/PD) studies in critically ill patients with ventilator-associated pneumonia and healthy adipose volunteers with a body mass index ≥ 20 kg/m² showed that the recommended standard dose of 1 g may not provide adequate free, protein-unbound drug concentrations in plasma of these special populations. Moreover, no published data are available on the effect of renal replacement therapy on the elimination of ertapenem in critically ill patients with ARF. Secondly, in EDD-altered distribution characteristics of substances, longer treatment time, different filter types as well as varying blood and dialysate flow rates as compared to IHD affect the total amount of drugs that is removed. A recent study on total solute removal, dialyzer extraction ratios and total cleared volumes for urea, creatinine, phosphorus and beta2-microglobulin showed a higher efficiency for prolonged dialysis as compared to IHD [17]. Therefore dosing of drugs in EDD might considerably differ from standard three times weekly intermittent haemodialysis (IHD) or continuous renal replacement therapy (CRRT) [8–10]. Our data indicate that this also holds true for ertapenem. Mistry *et al.* [4] showed in outpatients with end-stage renal disease that the plasma clearance of ertapenem significantly increased on the dialysis day. A 4-h haemodialysis session immediately after a 1.0 g dose of ertapenem removed ~30% of the drug. Unfortunately, no data on the dialysis procedure of these five patients are available. In contrast to the data by Mistry *et al.*, our data indicate that ICU patients with sepsis undergoing EDD need 1.0 g ertapenem per day. This difference can be explained by the long treatment time (8 h), and possibly a more efficacious dialyzer might have contributed to the higher dialysis clearance in our study

(30.2 mL/min) as compared to 19 mL/min reported by Mistry *et al.* [4] As we have calculated the dialyzer clearance only at the beginning of the EDD, we cannot exclude a decrease in dialyzer clearance over time. Another limitation in pharmacokinetic analysis based on blood samples is the fact that partial filter absorption of carbapenems, which have been reported for meropenem, will lead to an overestimation of the dialyzer clearance. Moreover, the limited number of patients might lead to skewed view of the effect of haemodialysis on ertapenem elimination. Finally, the question arises: Are the free, protein-unbound ertapenem concentrations in plasma high enough to eliminate the bacteria effectively? Like other β -lactam antibiotics, carbapenems exert their killing effect in a time-dependent manner. In this category of antibacterial drugs, by increasing the concentrations above four to five times the MIC of the bacteria no longer adds a proportional increase in the killing effect. Therefore, maximum killing is obtained by optimizing the time of exposure of the drug to the bacteria so that the concentrations remain above the MIC as long as possible. The main pharmacokinetic/pharmacodynamic (PK/PD) parameter for β -lactams is the proportion of time of the dose interval during which the drug concentration exceeds the MIC ($T_{>MIC}$). For carbapenems, a $T_{>MIC}$ of 30–40% of the dose interval has been previously suggested to be effective due to their rapid bactericidal activity. *In vitro* studies demonstrated that ertapenem inhibited 90% (MIC₉₀) of methicillin-susceptible *Staphylococcus aureus* strains, *Streptococcus spp.* and extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae at ≤ 0.5 mg/L. MIC₉₀ values for penicillin-susceptible, penicillin-intermediate susceptible and penicillin-resistant *Streptococcus pneumoniae* strains were 0.03, 0.5 and 2.0 mg/L, respectively. Against most anaerobe bacteria, ertapenem had a minimal inhibitory concentration of ≤ 1.0 mg/L and against non-ESBL-producing Enterobacteriaceae MIC₉₀ values ranged from 0.03 to 0.06 mg/L. In our study, estimated protein-unbound ertapenem plasma concentrations 24 h after a single intravenously administration of 1 g were 1.3 ± 1.0 mg/L. As this study in ICU patients with acute renal insufficiency undergoing extended daily dialysis demonstrates, a dose of 1 g

once a day results in plasma free drug levels higher than MICs of most above-mentioned pathogens (MIC₉₀ ≤1 mg/L) for the entire dosing interval (Figure 2). In addition, free ertapenem concentrations exceeded MIC₉₀ values of penicillin-resistant *Pneumococci* as in frequently observed respiratory tract pathogens for >20 h (~85% of the dosing interval) after the start of infusion.

In summary, although a firm recommendation of a dosing regime is not possible based on our single-dose PK data, to give 1 g ertapenem per day to critically ill patients with ARF in the ICU that undergo EDD is necessary to ensure optimal free concentrations of ertapenem. A reduction of the dose, as suggested by the manufacturer, is not supported by our data. Further dosing recommendations for patients with renal failure in the ICU treated with such effective modes of renal replacement therapy should be developed to avoid excess mortality due to under-dosing of life-saving medication.

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