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BRIEF REPORT

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Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator-associated pneumonia

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Abstract *Objective:* We conducted a prospective, open-label study to determine the steady-state serum and epithelial lining fluid (ELF) concentrations of unbound ertapenem administered once daily to critically ill patients with early-onset ventilator-associated pneumonia (VAP). *Design and setting:* Prospective, open-label study in an intensive care unit and research ward in a university hospital. *Patients:* Fifteen patients with VAP received 1-h intravenous infusions of 1 g ertapenem once daily. *Interventions:* After 2 days of therapy the steady-state serum and ELF concentrations of free ertapenem were determined by high-performance liquid chromatography. *Measurements and results:* The median (interquartile range) free ertapenem peak (C_{max}), intermediate (C_{12}), and trough (C_{min}) concentrations (mg/l) 1, 12, and 24 h after the end of infusion were 30.3 (27.1–37.8), 4.8 (3.9–6.4), and 0.8 (0.5–1.2) in serum and 9.4 (8.0–10.7), 2.0 (1.1–2.5), and 0.3 (0.2–0.4) in ELF, respectively, showing a median free ertapenem percentage penetration in ELF of approx. 30%. The median (interquartile range) serum area under concentration-time curve of free ertapenem during the observational period was 226.7 mg h^{-1} l^{-1} (202.2–263.9). *Conclusion:* Our study shows satisfactory results, with unbound ertapenem concentrations both in serum and ELF exceeding the MIC_{90} values of most of the causative pathogens encountered in early-onset VAP during 50–100% time. This suggests that 1 g intravenous ertapenem administered once daily should be effective during the treatment of early-onset VAP in critically ill patients with no known risk factors for multidrug-resistant pathogens.

Keywords Ertapenem · Pharmacokinetics · Lung diffusion · Intensive care · Early-onset · Ventilator-associated pneumonia

Introduction

Ertapenem is a new carbapenem, exhibiting activity against most Gram-positive and Gram-negative aerobic and anaerobic bacteria commonly recovered from community-acquired infections, including extended-spectrum β-lactamase-producing pathogens [1, 2, 3]. Ertapenem has recently been proposed by the American Thoracic Society as initial empirical therapy for hospital-acquired or early-onset ventilator-associated pneumonia (VAP) in patients with no known risk-factors for multidrug-resistant pathogens [4]. Although the efficacy of ertapenem has been studied in various in vitro models or in patients with community-acquired pneumonia, no pharmacokinetic data concerning critically ill patients on mechanical ventilation with early-onset VAP are available [3, 5, 6].

It has been shown that the efficacy or ertapenem is correlated with the time during which free concentration is above the minimum inhibitory concentration (MIC) of the responsible pathogen [3]. Moreover, using serum concentrations may frequently overestimate the target

site concentrations and therefore clinical efficacy [7]. Although the concentration of ertapenem in epithelial lining fluid (ELF), which has been advocated as a reliable marker of extracellular lung concentrations, has previously been studied in patients undergoing lung surgery, no data are available in critically ill patients on mechanical ventilation [8, 9, 10]. Therefore we conducted a study to determine the steady-state serum and ELF free concentrations and pharmacokinetic parameters of 1 g intravenous ertapenem administered once daily to critically ill patients with early-onset VAP. The results of this study were presented in part in abstract form at the 24th ICAAC, Washington, 2005 (abstract A2937).

Materials and methods

This was a prospective, open-label, single-center study approved by the local ethics committee. Prior to inclusion in the study all patients or their closest relative provided written informed consent. Critically ill adult patients on mechanical ventilation were considered for inclusion when suspected of having early-onset VAP with no known risk factors for multidrug resistant pathogens (i.e., duration of ventilation less than 4 days and no previous antibiotic therapy at the time of inclusion) [4]. The patients were excluded from the study if they were allergic to carbapenem antibiotics or exhibited renal dysfunction defined by a calculated creatinine clearance (using the urine of 24 h) less than 40 ml/min. Fifteen adult subjects with early-onset VAP completed the study (Table 1).

Before initiation of therapy, specimens for microbiological diagnosis were obtained using a plugged telescoping catheter (Combicath, Plastimed, St-Leu-La-Forêt, France) from all patients, as previously described [11]. All subjects received 1-h intravenous infusions of 1 g ertapenem once daily. All samples for free ertapenem concentration determinations were obtained at steady-state after 2 days of therapy. For the determination of peak, intermediate and trough serum concentrations (C_{max}, C_{12} and C_{min}), blood samples were collected 1, 12, and 24 h after the end of infusion and were immediately centrifuged at 3,000 rpm for 5 min. The serum was removed and stored at –80 °C until analyzed. Each subject underwent simultaneously to blood sampling 1, 12, or 24 h after the end of infusion one standardized bronchoalveolar microlavage (mini-BAL) procedure, as previously described [12, 13, 14]. A standard bronchial brush tube (Combicath) was inserted in the endotracheal tube and used to perform a mini-BAL with 40 ml sterile 0.9% normal saline solution. The aspirate was immediately centrifuged at 3,000 rpm for 5 min, and a single aliquot of supernatant was separated and frozen for the urea assay. The remaining volume was frozen at –80 °C until the assays were performed. All blood and BAL samples were assayed within 6 months from the time of their collection.

Table 1 Patient characteristics at enrollment ($n = 15$) (*SAPS II* Simplified Acute Physiology Score II [19])

Age, median (years; IQR)	62 (49–70)
Gender: M/F	9/6 (60%/40%)
Weight, median (kg; IQR)	66 (58–78)
SAPS II, median (IQR)	23 (18–28)
Creatinine clearance, median (ml/min; IQR)	74 (66–109)
Albumin, median (g/l; IQR)	32.6 (28.1–39.4)
Main diagnosis	
Trauma	8 (53%)
Abdominal surgery	4 (27%)
Pancreatitis	3 (20%)
PaO_2/FIO_2 ratio (mmHg; IQR)	284 (229–299)

Free ertapenem concentrations (obtained after ultrafiltration) in serum and BAL were measured simultaneously by a high-performance liquid chromatography method validated in our laboratory [15]. The method used ultraviolet detection set at a wavelength of 305 nm and a separation on a Prontosil AQ C18 column, with imipenem used as an internal standard. This assay was linear over the concentration range of 0.5–100 and 0.25–50 μg/ml in serum and BAL, respectively. Limits of detection and of quantification were 0.05 and 0.25 μg/ml, respectively. Validation data for accuracy and precision were coefficient of variation less than 2.48% and 8.25%, respectively, and accuracy in the range 98.1–104.2% and 102.2–108.4%, respectively, for intra- and inter-day.

As previously described, the concentration of free ertapenem in ELF (ETP_{ELF}) was determined as follows, using urea as an endogenous marker [14, 16]: $ETP_{ELF} = ETP_{BAL} \times urea_{SER}/urea_{BAL}$, where ETP_{BAL} is the measured concentration of free ertapenem in BAL fluid, $urea_{SER}$ is the concentration of urea in serum and $urea_{BAL}$ is the concentration of urea in the BAL fluid.

Individual patient steady-state concentration-time data were analyzed with an open one-compartment model with first-order elimination from central compartment using the SIPHAR software package (Simed, Créteil, France). The pharmacokinetic parameters determined directly from observed individual profiles using a pharmacokinetic population approach and Bayesian estimators of ertapenem previously determined in a population of intensive care unit patients (PASTRX program in USC*PACK PC Clinical Programs, R. Jelliffe, University of Southern California, Los Angeles, Calif., USA) were the elimination rate constant (K_{el}), elimination half-life ($t_{1/2}$), volume of distribution (VD), total body clearance (CL_T), and area under the serum concentration-time during the observational period ($AUC_{0–24}$).

Table 2 Steady-state individual pharmacokinetic parameters and serum and ELF concentrations of unbound ertapenem ($t_{1/2}$ elimination half-life, VD volume of distribution, CL_T total body clearance, AUC_{0-24} area under concentration-time curve during the observational period, C_{max} peak serum concentration 1 h after the end of infusion, C_{12} serum concentration 12 h after the end of infusion, C_{min} trough serum concentration 24 h after the end of infusion, ELF epithelial lining fluid, BAL bronchoalveolar lavage)

Patient no.	$t_{1/2}$(h)	VD (l)	CL_T (l/h)	AUC_{0-24} (mg h^{-1} l^{-1})	C_{max} (mg/l)		C_{12} (mg/l)		C_{min} (mg/l)		Concentration ratios	
					Serum	ELF	Serum	ELF	Serum	ELF	Ertapenem ELF/serum	Urea BAL/serum
1	7.5	41.1	3.8	262.0	51.5	10.8	4.8	–	0.5	–	0.21	15.4
2	6.4	19.0	2.1	485.3	30.3	7.7	6.3	–	0.9	–	0.25	12.8
3	8.0	55.8	4.8	206.9	16.9	10.6	3.8	–	1.2	–	0.63	5.6
4	8.2	57.6	4.9	200.6	26.8	8.1	4.1	–	1.0	–	0.30	4.7
5	4.6	31.1	4.7	213.1	29.2	9.4	4.3	–	0.5	–	0.32	9.6
6	12.0	100.0	5.8	173.1	36.1	–	1.7	0.9	0.8	–	0.51	2.8
7	10.0	47.2	3.3	305.4	33.6	–	9.3	3.1	0.4	–	0.33	4.4
8	8.0	40.0	3.5	288.7	27.9	–	6.4	2.0	0.6	–	0.31	9.0
9	12.0	67.2	3.9	255.2	38.4	–	3.2	1.1	1.2	–	0.34	11.1
10	8.0	50.6	4.4	226.9	29.7	–	4.9	2.3	1.2	–	0.47	6.8
11	7.5	47.7	4.4	226.7	22.9	–	6.9	–	0.6	0.1	0.22	14.0
12	8.5	71.7	5.9	171.1	39.8	–	5.8	–	0.4	0.3	0.46	8.3
13	9.0	57.7	4.4	225.1	35.6	–	8.9	–	1.4	0.4	0.28	9.0
14	6.3	54.8	6.0	165.9	22.5	–	3.3	–	0.7	0.2	0.29	6.8
15	6.1	34.5	3.8	263.2	38.3	–	4.1	–	0.9	0.4	0.44	9.5
Median	8.0	50.6	4.4	226.7	30.3	9.4	4.8	2.0	0.8	0.3	0.32	9.0
IQR	6.7–8.9	40.3–56.7	3.8–4.9	202.2–263.9	27.1–37.8	8.0–10.7	3.9–6.4	1.1–2.5	0.5–1.2	0.2–0.4	0.28–0.46	5.9–10.7

Results

Of the 15 patients 12 had one organism recovered using the plugged telescoping catheter technique, all susceptible to ertapenem (7 *Streptococcus pneumoniae*, 5 Enterobacteriaceae, and 3 oxacillin-susceptible *Staphylococcus aureus*). All patients but one (93.3%) treated with ertapenem had favorable outcome after 10 days of therapy. A superinfection on day 5 of therapy caused by oxacillin-resistant *S. aureus* occurred in one patient for whom no causative pathogen was initially recovered, successfully treated after 10 days of vancomycin. The median (interquartile range) free ertapenem peak (C_{max}), intermediate (C_{12}), and trough (C_{min}) concentrations (mg/l) 1, 12, and 24 h after the end of infusion were 30.3 (27.1–37.8), 4.8 (3.9–6.4), and 0.8 (0.5–1.2) in serum and 9.4 (8.0–10.7), 2.0 (1.1–2.5), and 0.3 (0.2–0.4) in ELF, respectively (Table 2), showing a percentage penetration in ELF of approx. 30–40%.

Discussion

The pharmacokinetics/pharmacodynamics and tissue penetration of ertapenem have been studied in various in vitro and human models [1, 2, 3, 6, 9, 10, 17]. However, these studies were generally carried out in healthy volunteers, and only few pharmacokinetic data concerning infected or critically ill patients are available, which may present pathophysiological conditions influencing the pharmacokinetic profile of ertapenem.

This is the first study to report the steady-state serum and ELF concentrations and the ELF percentage penetration of 1 g unbound ertapenem administered once daily to critically ill patients with early-onset VAP. Similar to other β-lactams, the pharmacodynamic parameter best correlated with clinical efficacy for carbapenem antibiotics is the fraction of the dosing interval when the drug concentration exceeds the MIC ($t_{>MIC}$) of the causative pathogen [2, 3, 10]. It has been reported that the $t_{>MIC}$ required for bacteriostasis in vivo is 30% of the dosing interval for carbapenems [3, 10]. The minimum percentage of $t_{>MIC}$ needed for optimal effect is known in animals (30–50%) but not in humans; it is probably less than 100% but may be higher than 50% [8, 18]. Considering this pharmacokinetic/pharmacodynamic parameter as predictive of outcome, our study shows satisfactory results, with unbound ertapenem concentrations in both serum and ELF exceeding the MIC_{90} values of most of the causative pathogens encountered in early-onset VAP (0.25–2 mg/l for *S. pneumoniae*, 0.06–0.125 mg/l for *Haemophilus influenzae*, 0.25–0.5 mg/l for oxacillin-susceptible *S. aureus*, and 0.03–0.125 mg/l for Enterobacteriaceae) and anaerobes (0.5–1 mg/l) during 50–100% time [4, 5]. This suggests that 1 g intravenous ertapenem administered once daily should be effective during the treatment of early-onset VAP in critically ill patients with no known risk factors for multidrug-resistant pathogens.

Our study, however, presents some limitations. First, the relatively small number of patients does not permit extrapolation to any critically ill patient with early-onset VAP, who might present different renal functions or underlying conditions influencing the serum and tissue distribution of ertapenem. Moreover, our results may not be applied to any population, such as morbidly obese or pediatric patients. In addition, local epidemiology of causative pathogens encountered in early-onset VAP, and their susceptibility pattern to ertapenem should be known before administering this agent as empirical therapy, since narrower-spectrum and less expensive agents may be proposed as first-line therapy depending on local conditions.

Conclusion

Our study shows that the intravenous administration of ertapenem 1 g once daily to critically ill patients with early-onset VAP and no known risk factors for multidrug resistant pathogens provides satisfactory pharmacokinetic results in this particular subset of patients, with a free ertapenem percentage penetration in ELF of approx. 30–40% and concentrations exceeding the MIC of the targeted pathogens in both serum and ELF during 50–100% of time. This suggests that 1 g intravenous ertapenem administered once daily should be effective during the treatment of early-onset VAP caused by sensitive pathogens. Further studies are required to evaluate the clinical, microbiological, and economic impact of ertapenem in this indication.

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