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Pharmacokinetics of ertapenem in outpatients with complicated urinary tract infections

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Objectives: Ertapenem is a broad-spectrum carbapenem antibiotic used to treat severe bacterial infections. In view of its dosing convenience, it is increasingly used as outpatient therapy. The objective of this study was to determine the pharmacokinetics and renal disposition of ertapenem in outpatients with complicated urinary tract infections.

Methods: Ertapenem was administered as a daily intravenous infusion of 1 g over 30 min. At steady-state, blood and urine samples were collected over one dosing interval. Drug concentrations in serum and urine were determined using a validated liquid chromatography–tandem mass spectrometry method. A population pharmacokinetic model was used to characterize ertapenem serum and urine profiles. The likelihood of the standard dosing achieving a favourable pharmacokinetic–pharmacodynamic exposure was evaluated using Monte Carlo simulations.

Results: Ten adult male patients were studied. Concentration–time profiles of ertapenem in both serum ($r^2 = 0.997$) and urine ($r^2 = 0.982$) were captured satisfactorily. Mean values for volume of distribution, clearance and elimination $t_{\frac{1}{2}}$ were 4.8 L, 0.7 L/h and 6.1 h, respectively. A high ertapenem concentration (>128 mg/L) could be attained in the urine at 40% of the dosing interval.

Conclusions: The pharmacokinetics of ertapenem in serum and urine were characterized. Our simulations suggested that a sufficiently high ertapenem concentration could be achieved in urine to overcome low to intermediate resistance. Clinical investigations to validate our findings are warranted.

Keywords: population modelling, maximum likelihood expectation maximization, Monte Carlo simulation

Introduction

Ertapenem is a carbapenem antibiotic commonly used to treat complicated intra-abdominal infections, skin and skin structure infections, community-acquired pneumonia, complicated urinary tract infections and acute pelvic infections.[1] Ertapenem has excellent *in vitro* activity against a broad range of Gram-negative and Gram-positive bacteria, including extended-spectrum β-lactamase-producing Enterobacteriaceae.[2–4]

In view of its favourable pharmacokinetic properties and safety profile, ertapenem is an attractive therapeutic option for infections due to susceptible bacteria after an initial clinical improvement has been observed in the hospital. The reported $t_{\frac{1}{2}}$ of ertapenem is considerably longer than most β-lactams used in clinical practice, which increases the feasibility of using it in outpatients. When an oral therapeutic option is not available for a stable patient, intravenous ertapenem is typically administered once daily in the outpatient setting to complete the prescribed treatment course. The feasibility and patient acceptance of this cost-effective approach has previously been demonstrated in Singapore.[5,6] In view of the excellent efficacy reported,[7] ertapenem is a frequently used antibiotic for the treatment of complicated urinary tract infections in our outpatient parenteral antimicrobial therapy (OPAT) units.

Carbapenem resistance among Gram-negative bacteria has been reported locally in Singapore[8,9] and its prevalence is increasing worldwide.[10,11] It is a major concern among clinicians, as the clinical utility of these first-line agents is threatened. Unfavourable clinical outcomes associated with reduced carbapenem susceptibility have been reported and reviewed previously.[12–14]

The pharmacokinetics of ertapenem have been investigated previously, mostly in healthy subjects.[15–17] Since a substantial proportion of the dose is expected to be renally eliminated unchanged, the high drug concentration achieved in the urine could potentially overcome pathogens confined to the urinary tract that have a low to intermediate level of ertapenem resistance. However, the detailed renal disposition of ertapenem in outpatients with complicated urinary tract infections has not been published, and the likelihood of pharmacokinetic–pharmacodynamic target attainment at the site of infection is not well established.

The objective of this study was to examine the pharmacokinetics and renal disposition of ertapenem in outpatients with complicated urinary tract infections. The results could provide supportive evidence for the rational use of ertapenem.

Patients and methods

Study sites

This study was conducted in the National University Hospital and Tan Tock Seng Hospital OPAT centres, two university-affiliated teaching hospitals in Singapore. Patients were enrolled between March 2011 and February 2013.

Study design

This was a prospective, open-label, observational, pharmacokinetic study. The study was approved by the Domain Specific Review Board. Written informed consent was obtained from all participants prior to study enrolment.

Study population

Adult patients (age range 21–80 years) with normal renal function or mild renal impairment (creatinine clearance >30 mL/min), diagnosed with a complicated urinary tract infection and prescribed ertapenem as OPAT were considered for study enrolment. The exclusion criteria were hypersensitivity to ertapenem, overweight or underweight (defined as body mass index <15 or >30 kg/m^2), baseline serum creatinine >2 mg/dL (176 μmol/L), acute renal failure, pregnancy, participation in another interventional clinical investigation within 30 days, and inability to obtain informed consent. Ertapenem was administered as a daily intravenous infusion of 1 g over 30 min.

Sample collection

When steady-state was achieved (presumed to be after the third dose), four blood samples and three urine samples were collected over one dosing interval for each participant. One blood sample was collected immediately prior to drug administration and three blood samples were taken at ∼2, ∼10 and ∼23.5 h after the end of drug infusion. The subjects were asked to void before drug administration and three aliquots of urine were collected cumulatively at ∼2, ∼10 and ∼23.5 h after drug administration was completed. A new empty bottle for collecting urine was used for each aliquot and the volume of urine collected was recorded. After a sample had been taken from each aliquot, the urine samples (collected over 24 h) were pooled to verify creatinine clearance. All samples collected were specifically timed in relation to the dose given.

Drug assay

Ertapenem concentrations in serum and urine were assayed using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. The LC–MS/MS system consisted of an Agilent 1290 UHPLC equipped with a cooled auto-sampler (6°C) connected to an Agilent 6460 triple quadrupole mass spectrometer (Agilent Technologies, Waldbronn, Germany). Chromatographic separations were achieved using ZORBAX Eclipse Plus C_{18} Rapid Resolution HD (Agilent, 50 mm×2.1 mm, 1.8 μm) with a gradient elution. Mobile phase A and B were water and 90% (v/v) acetonitrile, respectively, both containing 0.1% formic acid. The flow rate was 0.5 mL/min and the elution of the mobile phase was set as follows: 0–0.5 min, 15% B; 0.5–1.5 min, 15%–90% B; and 1.5–2 min, 90% B. After each injection there was a 0.5 min interval for the mobile phase to revert to the initial 15% B. The mass spectrometer was operated under positive ionization mode. The detection of ertapenem and ertapenem-d4 was based on multiple-reaction monitoring of mass-to-charge ratio (m/z) 476.2→432.1 and 480.2→436.1, respectively. The source temperature, drying gas (N_2) flow rate, nebulizer pressure, sheath gas temperature, sheath gas flow rate and capillary voltage were set at 300°C, 10 L/min, 45 psi, 300°C, 11 L/min and 5000 V, respectively.

Ertapenem and its deuterium-labelled internal standard ertapenem-d4 were purchased from ALSACHIM (Illkirch-Graffenstaden, France) and prepared in methanol at 10 and 1 mg/mL, respectively, as standard stock concentrations. Calibrations of ertapenem in serum and urine, 1–200 and 10–2000 mg/L, respectively, were prepared by spiking the ertapenem standard stock solution in blank serum or urine followed by serial dilution. Serum and urine calibration samples were then mixed with two times and equal volumes, respectively, of 0.1 M 2-(4-morpholino)ethylsulfonic acid buffer

Table 1. Pertinent patient information and derived pharmacokinetic parameters

Subject	Age (years)	Gender	Weight (kg)	CL_{CR} (mL/min)	Diagnosis	*V* (L/kg)	CL (L/h)
1	66	male	66.5	74	catheter-related UTI	0.042	0.419
2	67	male	65.9	48	UTI, BPH	0.064	0.662
3	66	male	77.3	46	bladder stone	0.087	0.805
4	68	male	64	73	UTI, BPH	0.060	0.498
5	58	male	83.5	130	prostate abscess	0.063	0.859
6	52	male	49.1	32	pyelonephritis	0.106	0.883
7	60	male	70.1	103	prostatitis	0.041	0.513
8	75	male	79.4	63	prostatitis	0.039	0.445
9	44	male	92.8	136	prostatitis	0.083	1.176
10	64	male	86.5	119	prostatitis	0.077	0.947
Mean	62		73.5	82.4		0.066	0.721

CL_{CR}, creatinine clearance; *V*, volume of distribution; CL, total drug clearance; UTI, urinary tract infection; BPH, benign prostatic hypertrophy.

(pH 6.5). Serum samples were mixed with two times the volume of methanol/acetonitrile (1:1, v/v) containing 2 mg/L ertapenem-d4 for protein precipitation, followed by centrifugation at 13000 **g** for 10 min. Two microlitres of the supernatant was injected into the LC–MS/MS system for analysis. Urine samples were diluted 20 times with 0.1% formic acid containing 2 mg/L ertapenem-d4 and 2 μL was injected for analysis. Concentrations of ertapenem in the serum and urine samples were back-calculated from the weighted ($1/x^2$) linear least squares fitted lines of peak area ratio (ertapenem to internal standard ertapenem-d4) versus concentrations. Intra-day and inter-day variability of this assay were <4% and <5%, respectively.

Pharmacokinetics

Ertapenem serum concentration–time profiles and cumulative drug recovery from urine were co-modelled using the maximum likelihood expectation maximization population modelling module in ADAPT 5.[18] Both one-compartment and two-compartment models were explored. Initial values were based on the mean and standard deviation of parameters estimated for each patient using the standard two-stage approach. Based on the assay variance, two separate linear variance model equations were adopted for measurements of serum concentration and drug amount recovered in urine. Model fits were assessed using the residual sum of squares, bias and precision of the best-fit values. These two structural models were discriminated using the final objective function; the likelihood ratio test with two degrees of freedom was used. Correlations of selected model parameters to pertinent demographic variables (i.e. covariates) were explored.

Monte Carlo simulations

The steady-state drug concentration profile for serum and the amount of drug recovered from urine over a dosing interval in 1000 subjects (receiving a daily intravenous infusion of 1 g of ertapenem over 30 min) were simulated using ADAPT 5. The mean and covariance matrix of the best-fit parameter estimates from population modelling were used as priors, assuming normal distribution. The probability of free (unbound) serum drug concentration above different MICs for 40%, 70% and 100% of the dosing interval was assessed. Protein binding was assumed to be 95%.[16] A concentration–time profile for urine was also simulated for each subject by dividing the active drug (50% of the recovered component) with the cumulative urine output (assumed to be 70 mL/h). Two hypothetical scenarios were considered: (i) patients did not void for 9.6 h; and (ii) patients voided once, 4.8 h after starting the infusion. The drug concentration in urine at 9.6 h after initiation of administration (40% of dosing interval) was compared with various MICs.

Results

Patient demographics

A total of 11 Asian male patients were enrolled for this study. However, one patient was excluded from the data analysis because of abnormal renal function (creatinine clearance <30 mL/min). Creatinine clearance and age of the 10 evaluable patients were 82.4 ± 37.2 mL/min (mean ± SD) and 62 ± 9 years, respectively. Pertinent demographics are shown in Table 1. The clinical outcomes of these patients are the focus of another study (data not shown).

Pharmacokinetics

A total of 39 serum and 29 urine samples were obtained and analysed. Approximately 76.8% of the daily ertapenem dose (mean value for all patients) was recovered cumulatively from urine.

Table 2. Best-fit pharmacokinetic parameter values

	Kr (1/h)	Knr (1/h)	Vc (L)	Kcp (1/h)	Kpc (1/h)
Mean	0.337	0.101	1.864	0.998	0.738
Covariance matrix					
Kr	0.019				
Knr	−0.005	0.005			
Vc	−0.120	0.022	0.981		
Kcp	−0.042	−0.010	0.359	0.260	
Kpc	−0.068	−0.002	0.544	0.335	0.461

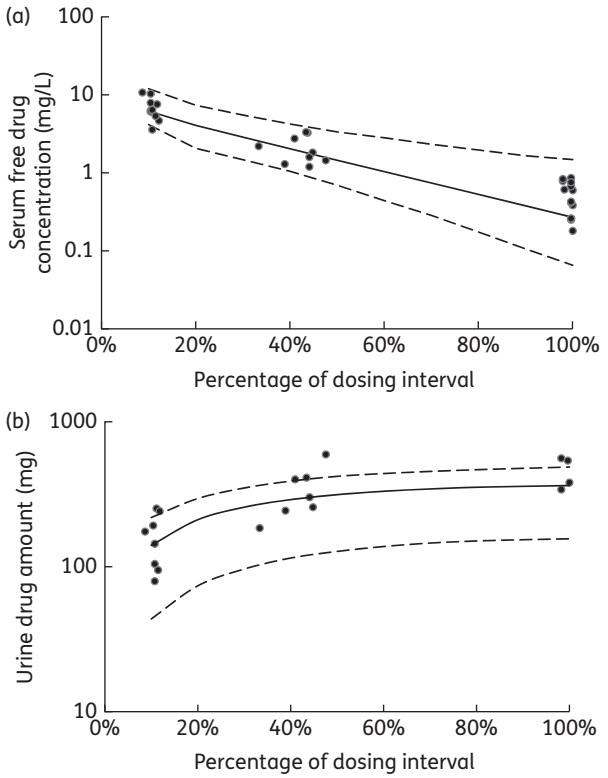

Figure 1. Simulated steady-state ertapenem concentration–time profiles for serum (a) and the amount of active drug recovered in urine (b). The continuous lines represent the median profiles, the broken lines represent the 95% CIs and the filled circles represent the observed data.

Both model fits (one-compartment or two-compartment) to the data were satisfactory, but the two-compartment model was preferred. Elimination $t_{\frac{1}{2}}$, total volume of distribution and total clearance of ertapenem were 6.1 ± 1.2 h, 4.8 ± 1.8 L and 0.7 ± 0.3 L/h, respectively. The mean and covariance matrix of the best-fit model parameters are shown in Table 2; pertinent secondary parameters are shown in Table 1. In our sample population, we did not find a significant correlation between creatinine clearance and total drug clearance.

Monte Carlo simulations

Typical drug concentration–time profiles for serum and urine (no voiding) from 1000-subject simulations are shown in Figure 1.

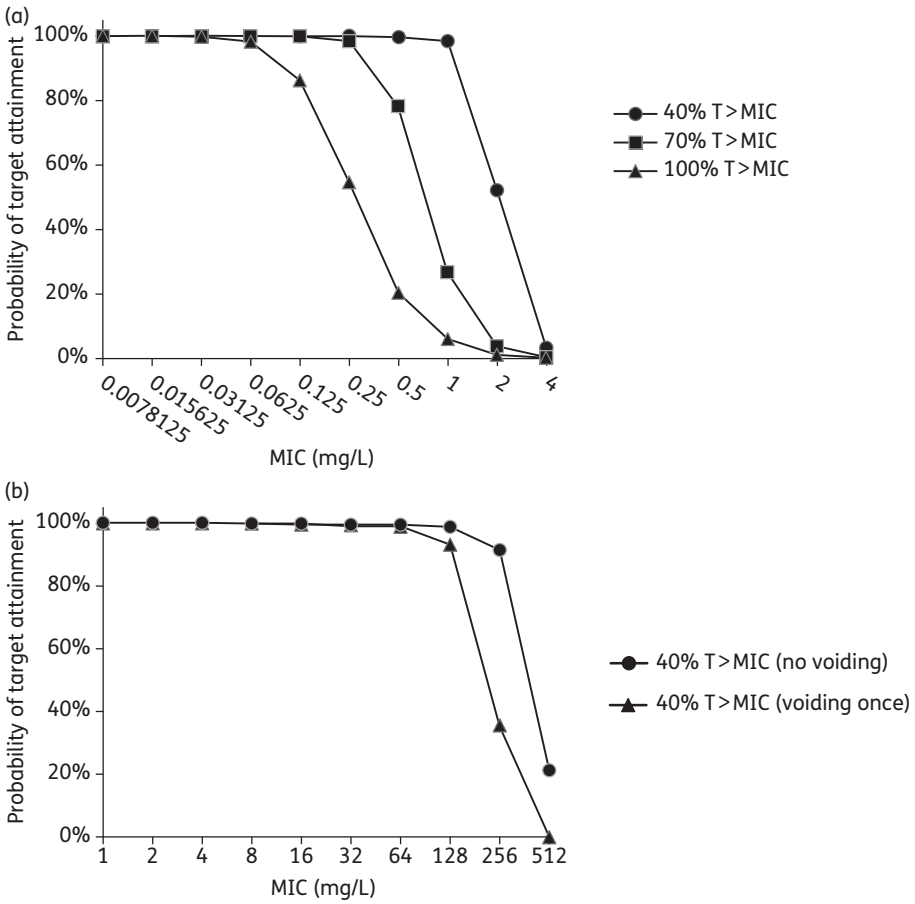

Figure 2. Probability of achieving various pharmacokinetic–pharmacodynamic targets in serum (a) and in urine (b).

Using the standard dose, the probabilities of achieving various pharmacokinetic–pharmacodynamic targets in serum and urine are shown in Figure 2. For serum concentration–time profiles, a good probability of target attainment (>80%) could be achieved for MICs of 1 mg/L, 0.25 mg/L and 0.125 mg/L, using T>MIC 40%, 70% and 100% of the dose interval, respectively. Since a much higher drug concentration can be anticipated in the urine, T>MIC 40% of the dose interval could probably be attained with MICs up to 128 mg/L (voiding once) and 256 mg/L (no voiding).

Discussion

Ertapenem has been reported to be effective in patients with complicated urinary tract infections.[7] However, detailed information on the renal disposition of ertapenem in outpatients with complicated urinary tract infections is scarce. A quantitative assessment would provide the supportive evidence for rational and optimal use of this drug.

Several studies have evaluated the pharmacokinetics of ertapenem in humans,[15–17] and our results were generally consistent with previous reports. The total drug clearance observed was lower in our patients (0.7 versus 1.8 L/h), which could be attributed the age difference of the subjects.[16] Despite having a reasonably normal baseline creatinine level, the renal function of our patients (mean age >60 years) might not have been as good as that of young healthy volunteers. The volume of distribution observed in our patients was also lower (4.8 versus 7.0 L). The difference could be due to the generally smaller body size of Asian patients. With a relatively small sample size in our study, the difference could also be the result of one or two individual outliers affecting the overall findings.

We briefly explored pharmacokinetic–pharmacodynamic target attainments with the standard ertapenem dosing in our patients. Using a commonly reported target (serum concentration above the MIC for 40% of the dose interval) for carbapenems against Gram-negative bacteria,[17,19] the probabilities of target attainment were 98.5% when the MIC was 1 mg/L and 52.2% when the MIC was 2 mg/L. Using an acceptable target attainment rate of ≥80%, our breakpoint threshold was marginally (one dilution tube) higher than the ertapenem breakpoint for Enterobacteriaceae reported by EUCAST (0.5 mg/L for susceptible and 1 mg/L for resistant strains).[20] The apparent discrepancy was probably due to the higher drug exposure observed in our patients, as explained above. Since ertapenem is dosed every 24 h, assessment using more conservative targets is also provided if one is concerned with the extended time that serum concentration is below the MIC.

As we anticipated, a significant proportion of the administered dose could be recovered in the urine of patients with complicated urinary tract infections. To put the data in practical terms useful to

front-line clinicians, two hypothetical scenarios were assumed to simulate the drug concentration–time profiles for urine. At 40% of a dose interval, a high ertapenem concentration (>128 mg/L) could be achieved. Thus even in urinary tract infections due to pathogens with reduced susceptibility, satisfactory therapeutic responses could be expected in patients using the standard ertapenem dosing.

There were several limitations with this study. First, only a limited number of subjects were studied. A more diverse subject population (in age, ethnicity and gender) would have enhanced the robustness of our results. The second limitation was the lack of obese patients. Obese patients might require a higher dose to achieve an adequate drug exposure. Furthermore, a mean 76.8% of the ertapenem dose was recovered from the urine in 24 h, consistent with the total drug recovery (74.2%) reported previously.[21] However, it was reported that approximately half the recovered drug from the urine was a pharmacologically inactive derivative, formed by hydrolysis of the β-lactam ring. The apparently high drug recovery in our study suggested that the analytical method used could not effectively distinguish the inactive metabolite from the parent ertapenem. Therefore, in the pharmacokinetic simulations, only 50% of the drug recovered in the urine was used to derive the concentration–time profiles. Finally, some assumptions were empirically made in the simulation of drug concentration–time profiles for urine. Deviations in the frequency, timing of voiding and urine production rate from our assumptions could have had a non-trivial impact on the pharmacokinetic simulations.

Conclusions

Our results showed promising evidence that the standard dosing of ertapenem would be effective in complicated urinary tract infections, even with pathogens of low to intermediate ertapenem resistance. Clinical investigations in outpatients are warranted to validate our findings.

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References

1 Keating GM, Perry CM. Ertapenem: a review of its use in the treatment of bacterial infections. *Drugs* 2005; **65**: 2151–78.

2 Livermore DM, Sefton AM, Scott GM. Properties and potential of ertapenem. *J Antimicrob Chemother* 2003; **52**: 331–44.

3 Shah PM, Isaacs RD. Ertapenem, the first of a new group of carbapenems. *J Antimicrob Chemother* 2003; **52**: 538–42.

4 Wexler HM. *In vitro* activity of ertapenem: review of recent studies. *J Antimicrob Chemother* 2004; **53** Suppl 2: ii11–21.

5 Seetoh T, Lye DC, Cook AR *et al*. An outcomes analysis of outpatient parenteral antibiotic therapy (OPAT) in a large Asian cohort. *Int J Antimicrob Agents* 2013; **41**: 569–73.

6 Yong C, Fisher DA, Sklar GE *et al*. A cost analysis of Outpatient Parenteral Antibiotic Therapy (OPAT): an Asian perspective. *Int J Antimicrob Agents* 2009; **33**: 46–51.

7 Wells WG, Woods GL, Jiang Q *et al*. Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by appropriate oral therapy. *J Antimicrob Chemother* 2004; **53** Suppl 2: ii67–74.

8 Balm MN, Ngan G, Jureen R *et al*. Molecular characterization of newly emerged bla_{KPC-2}-producing *Klebsiella pneumoniae* in Singapore. *J Clin Microbiol* 2012; **50**: 475–6.

9 Teo JW, La MV, Krishnan P *et al*. *Enterobacter cloacae* producing an uncommon class A carbapenemase, IMI-1, from Singapore. *J Med Microbiol* 2013; **62**: 1086–8.

10 Munoz-Price LS, Poirel L, Bonomo RA *et al*. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect Dis* 2013; **13**: 785–96.

11 Tzouvelekis LS, Markogiannakis A, Psichogiou M *et al*. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev* 2012; **25**: 682–707.

12 Ben-David D, Kordevani R, Keller N *et al*. Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections. *Clin Microbiol Infect* 2012; **18**: 54–60.

13 Correa L, Martino MD, Siqueira I *et al*. A hospital-based matched case–control study to identify clinical outcome and risk factors associated with carbapenem-resistant *Klebsiella pneumoniae* infection. *BMC Infect Dis* 2013; **13**: 80.

14 Hirsch EB, Tam VH. Detection and treatment options for *Klebsiella pneumoniae* carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. *J Antimicrob Chemother* 2010; **65**: 1119–25.

15 Majumdar AK, Musson DG, Birk KL *et al*. Pharmacokinetics of ertapenem in healthy young volunteers. *Antimicrob Agents Chemother* 2002; **46**: 3506–11.

16 Musson DG, Majumdar A, Holland S *et al*. Pharmacokinetics of total and unbound ertapenem in healthy elderly subjects. *Antimicrob Agents Chemother* 2004; **48**: 521–4.

17 Wiskirchen DE, Housman ST, Quintiliani R *et al*. Comparative pharmacokinetics, pharmacodynamics, and tolerability of ertapenem 1 gram/day administered as a rapid 5-minute infusion versus the standard 30-minute infusion in healthy adult volunteers. *Pharmacotherapy* 2013; **33**: 266–74.

18 D'Argenio DZ, Schumitzky A, Wang X. *ADAPT 5 User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software*. Los Angeles: Biomedical Simulations Resource, University of Southern California, 2009.

19 Cardone KE, Grabe DW, Kulawy RW *et al*. Ertapenem pharmacokinetics and pharmacodynamics during continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother* 2012; **56**: 725–30.

20 EUCAST. *Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 4.0, 2014*. http://www.eucast.org/clinical_breakpoints/ (2 March 2014, date last accessed).

21 Wong BK, Sahly Y, Mistry G *et al*. Comparative disposition of [^{14}C]ertapenem, a novel carbapenem antibiotic, in rat, monkey and man. *Xenobiotica* 2004; **34**: 379–89.