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Population pharmacokinetics and probability of target attainment of ertapenem administered by subcutaneous or intravenous route in patients with bone and joint infection

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Background: Ertapenem is a therapeutic option in patients with Gram-negative bone and joint infection (BJI). The subcutaneous (sc) route of administration is convenient in the outpatient setting and has shown favourable pharmacokinetics (PK), but available data on ertapenem are limited.

Objectives: To perform population PK analysis and pharmacokinetic/pharmacodynamic (PK/PD) simulation of ertapenem administered by the intravenous (iv) or sc route to patients with BJI.

Patients and methods: This was a retrospective analysis of PK data collected in patients with BJI who received iv or sc ertapenem. Measured ertapenem concentrations were analysed with a non-parametric population approach. Then, simulations were performed based on the final model to investigate the influence of ertapenem route of administration, dosage and renal function on the probability of achieving a pharmacodynamic (PD) target, defined as the percentage of time for which free plasma concentrations of ertapenem remained above the MIC ($fT_{>MIC}$) of 40%.

Results: Forty-six PK profiles (13 with iv and 33 with sc ertapenem) with a total of 133 concentrations from 31 subjects were available for the analysis. A two-compartment model with linear sc absorption and linear elimination best fitted the data. Creatinine clearance was found to significantly influence ertapenem plasma clearance. Simulations showed that twice daily dosing, sc administration and renal impairment were associated with an increase in $fT_{>MIC}$ and target attainment.

Conclusions: Our results indicate that 1 g of ertapenem administered twice daily, by the iv or sc route, may optimize ertapenem exposure and achievement of PK/PD targets in patients with BJI.

Introduction

Ertapenem is a therapeutic option for the treatment of bone and joint infection (BJI). It has been recommended for the treatment of prosthetic joint infection caused by Gram-negative organisms, especially Enterobacteriaceae.[1,2] This use is supported by favourable diffusion into bone and synovial tissue.[3]

The authorized routes for ertapenem administration are the intravenous (iv) and intramuscular (im) routes in the USA,[4] and only the iv route in Europe.[5] The recommended dose of ertapenem in patients with normal renal function is 1 g q24h. However, several treatment failures have been reported in patients treated with ertapenem at 1 g q24h iv for various infections,[6–8] which raises questions about the optimal dosage of this agent.

Prolonged therapy over several weeks or months is usually required for BJI. In such use, repeated iv administration of ertapenem may be complicated in the ambulatory care setting for

patients with limited venous access, such as elderly patients. Intramuscular administration is often painful and may be contraindicated because of co-administration of anticoagulant drugs. The subcutaneous (sc) route may be a convenient alternative for the administration of ertapenem in such situations.

In France, although it is still off-label usage, sc administration is not rare in geriatric patients for some antibacterial agents, including ceftriaxone, teicoplanin and ertapenem.[9,10] Frasca *et al.*[11] have compared the pharmacokinetic (PK) data for ertapenem administered by iv and sc routes in a limited series of six patients and showed that the sc route was associated with good bioavailability (99%±18%). Compared with the iv route, sc administration of ertapenem resulted in lower C_{max}, delayed maximal concentration and higher C_{min}. Our group has previously published its clinical experience with ertapenem used as salvage therapy for complicated BJI in a small group of 16 patients.[12] Compared with a 1 g twice daily iv administration of ertapenem, the same dosage regimen administered by the sc route was associated with significantly lower C_{max} and higher C_{min}. The outcome of sc ertapenem therapy was favourable in most patients.

As ertapenem is a time-dependent antibacterial, the published data, although limited, suggest that sc administration should not alter the drug effect compared with the reference iv administration. However, there has been no thorough assessment of the pharmacokinetics/pharmacodynamics (PK/PD) of sc ertapenem, and optimal dosage regimens of ertapenem for the treatment of BJI have not been examined so far.

The objectives of this study were to perform population PK analysis and PK/PD simulation of ertapenem in patients treated for BJI by the iv or sc route.

Patients and methods

Patient population and data collection

The study was a retrospective analysis of PK data collected in patients treated with ertapenem for BJI and followed up by the Lyon Reference Center for Complicated Bone and Joint Infections (Centre de Référence des Infections Ostéo-Articulaires complexes, CRIOAc). Patients included were previously enrolled in the Lyon BJI Cohort Study (ClinicalTrial.gov identifier NCT02817711). All patients who were treated from August 2010 to March 2014 and had at least one PK profile of ertapenem were included. Therapeutic drug monitoring (TDM) of ertapenem was performed regularly in these patients throughout therapy, on average every month, to ensure sufficient exposure and prevent drug accumulation. As there are no widely accepted targets for ertapenem TDM, the usual concentrations reported in the literature were used as rough guidance.[5,13]

Ertapenem was administered as a 30 min infusion given either iv or sc. The sc route was used in cases in which it was difficult to maintain venous access for prolonged therapy in an ambulatory care setting. Subcutaneous infusion was administered via a butterfly disposable needle in the lower quadrants of the abdomen or on the anterior side of a thigh. If there was a prosthetic hip joint, this was avoided and the injection was given in the corresponding thigh. In some patients, the route was switched from sc to iv or vice versa during ertapenem therapy, and PK data were collected for both routes. An ertapenem plasma concentration profile was determined on at least one occasion for each patient, and typically included trough, peak and 6 h post-dose level concentrations. Only two samples were obtained for three patients and only one for one patient on one occasion. These incomplete profiles were also included in the population analysis. All samples were obtained at the steady-state (>10 days after therapy onset or dose change) except for those of one patient. Data from this patient were analysed accordingly.

Ertapenem plasma concentrations were determined using an HPLC assay with a photodiode array detector as previously described.[14] This published method was used with minor modifications. Six calibration standards were prepared by spiking blank plasma to obtain calibration standards from 5 to 250 mg/L. Ertapenem concentrations were calculated at two wavelengths (306 and 330 nm). A spectral analysis was performed to check the purity of chromatographic peaks. Accuracy and precision were evaluated at three levels of quality control concentrations (7.5, 87.5 and 175 mg/L). For the period of the study, the inter-day imprecision was <6% with bias <5%. The lower limit of quantification was 1 mg/L.

Population PK analysis

Population PK modelling was performed using the non-parametric adaptive grid algorithm (NPAG) implemented in the Pmetrics R package (Laboratory of Applied Pharmacokinetics, Los Angeles, USA, www.lapk.org).[15,16] Ertapenem concentrations following sc and iv administration were modelled simultaneously. One- and two-compartment models were evaluated. Available covariates included sex, age, body weight, creatinine clearance (CL_{CR}) estimated by the original Cockcroft–Gault equation (based on actual body weight), glomerular filtration rate (GFR) estimated by the abbreviated Modification of Diet in Renal Disease (MDRD) equation, and concomitant use of glycopeptide and fluoroquinolone drugs.

The final model had two compartments plus an sc depot compartment with CL_{CR} influencing ertapenem plasma clearance. The ordinary differential equations describing the model were as follows:

$$\frac{dX_1}{dt} = R_{SC} - Ka \cdot X_1$$

$$\frac{dX_2}{dt} = R_{IV} + Ka \cdot X_1 - \frac{CL_{NR} + CL_S \cdot (CL_{CR} \times 0.06)}{Vd} \cdot X_2 - Kcp \cdot X_2 + Kpc \cdot X_3$$

$$\frac{dX_3}{dt} = Kcp \cdot X_2 - Kpc \cdot X_3$$

where X_1, X_2 and X_3 are the ertapenem amounts in the sc depot and central and peripheral compartments, respectively, R_{SC} and R_{IV} are the rates of administration by the sc and iv route, respectively (both equal to dose divided by infusion time, i.e. 0.5 h), *Ka* is the subcutaneous absorption rate constant (in h^{-1}), CL_{NR} is the non-renal clearance (in L/h), CL_S is the coefficient of renal clearance (in L/h per unit of CL_{CR}), CL_{CR} is creatinine clearance in mL/min, which is multiplied by 0.06 for conversion to L/h, and K_{cp} and K_{pc} are the intercompartment transfer rate constants (in h^{-1}). The last parameter is ertapenem apparent central volume of distribution, *V*d, which links ertapenem amount X_2 and concentration *C* as follows: $C = X_2/Vd$. Of note, R_{SC} and R_{IV} are positive during drug infusion and equal to zero after the end of infusion, and *Ka* has a value only for the sc route. We could not estimate the bioavailability (*F*) of ertapenem when administered by the sc route in this study, as bioavailability determination typically requires rich sampling and crossover design. Frasca *et al.*[11] estimated it at 99%±18%. Based on this result, we assumed that $F = 1$, and all disposition parameters are expressed irrespective of bioavailability for ease of reading throughout the article.

In Pmetrics, each measured concentration was weighted by 1/error.[2] The model describing the residual error was as follows:

$$error = \sqrt{(0.1259 + 0.0635.C + 0.0003C^2)^2 + \lambda^2}$$

where *C* is the observed concentration and λ is a parameter to be estimated by the algorithm. The first squared term is a polynomial describing the pattern of the ertapenem assay error. Its coefficients were estimated from calibration data for the assay technique.

Although ertapenem concentrations were measured on several occasions in some patients, intra-individual variability was not included in the

model, as this feature is currently not available in Pmetrics. This means that the same set of individual Bayesian posterior PK parameters was estimated over the entire ertapenem therapy for each patient. However, changes in ertapenem clearance as a consequence of change in renal function were taken into account.

Goodness of fit of candidate structural and covariate models were assessed using likelihood-derived criterion: the objective function [OF = −2 × log(*L*), where *L* is the likelihood] and Akaike information criterion [AIC = −2 log(*L*) + 2*p*]. The best model was the one that minimized the objective function and the AIC. Parameter values and plots of observed versus model-based predicted concentrations as well as residual plots were also examined. Bias and imprecision were derived from population and Bayesian posterior individual predictions. For each prediction–observation pair, we defined the prediction error as prediction minus observation and percent absolute error of prediction as absolute prediction error over observation. Bias was defined as the mean error of prediction (in mg/L), and imprecision as mean percent absolute error of prediction.

Internal, simulation-based model validation was performed as a visual predictive check (VPC). Each subject in the study population was used as a template for a 1000 subject simulation based on the population model. Model predictions were then visually compared with observed ertapenem concentrations.

Monte Carlo simulations and probability of target attainment

Monte Carlo simulations were performed based on the final model to investigate the influence of ertapenem route of administration (sc or iv), dosage and renal function on the probability of target attainment (PTA) at the steady-state. We used the semi-parametric simulation method available in Pmetrics, which respects the discrete non-parametric prior distribution estimated with NPAG. Three dosages of ertapenem were evaluated for both the sc and the iv route of administration: 1 g q24h, 1 g q12h and 2 g q24h. The infusion time was set at 30 min for all iv and sc simulations. In addition, three levels of renal function were considered: normal (100 mL/min), moderately impaired (50 mL/min) and severely impaired (25 mL/min). We assumed that the identified correlation between ertapenem clearance and CL_{CR} would hold true in patients with severe renal impairment. This assumption is supported by results of a study performed in patients with varying degrees of renal impairment.[17] A total of 18 dosage scenarios in terms of dosage/renal function were simulated, with 1000 virtual subjects for each. Steady-state PK profiles were obtained. Then, the PTA was derived for each condition. We considered an efficacy target, defined as the percentage of time during which free plasma concentrations of ertapenem remained above the MIC ($fT_{>MIC}$), of 40%, as suggested elsewhere.[18] A free fraction of 5% was assumed (i.e. 95% protein binding).[19] MIC values of 0.25, 0.5, 1, 2, 4 and 8 mg/L were tested, in accordance with the simulation study of Chen *et al.*[18] It is noteworthy that most Enterobacteriaceae have ertapenem MIC breakpoint values <1 mg/L according to EUCAST.[20]

Results

Population PK analysis

Forty-six PK profiles (13 with iv and 33 with sc ertapenem) from 31 subjects (21 male and 10 female; mean age, 58±16 years) with a total of 133 concentrations were available for the analysis. Table 1 shows the main characteristics of the study population.

A two-compartment model, with linear sc absorption and linear elimination best fitted the data. CL_{CR} was found to significantly influence ertapenem plasma clearance, resulting in a 13.5-point drop in the AIC compared with a base model without covariates. No other available covariate showed a significant influence on ertapenem PK. Of note, GFR estimated by the MDRD equation also improved the model fit, but to a lesser extent than CL_{CR}. The final estimates of population PK parameters are shown in Table 2.

Table 1. Characteristics of the study population

Characteristic	Value
Number of women/men	10/21
Age (years)[a]	58 (19–87)
Body weight (kg)[a]	75 (50–136)
Serum creatinine (μmol/L)	60 (31–115)
Creatinine clearance (Cockcroft–Gault equation, mL/min)[a]	127 (54–237)
Glomerular filtration rate (MDRD equation, mL/min/1.73 m^2)[a]	116 (56–218)
Ertapenem dosing regimen	sc/q12h, *n* = 13 sc/q24h, *n* = 7 iv/q12h, *n* = 9 iv/q24h, *n* = 1 iv/q36h, *n* = 1
Total number of measured ertapenem concentrations	133
Number of PK profiles by route	sc, *n* = 33 iv, *n* = 13
Number of measured ertapenem concentrations per subject	3 (1–12)

Except where indicated, data shown are median (minimum–maximum).
[a]Values recorded on the first therapeutic drug monitoring occasion.

The final model described the data very well, with little bias and imprecision, as shown in Figure 1. The VPC obtained after simulation with the final model is shown in Figure 2. One can see considerable agreement between observations and model-based predictions.

Monte Carlo simulations and probability of target attainment

Figure 3 shows the simulated PK profiles at the steady-state of ertapenem administered by the iv and sc routes as a 1 g q24h regimen. This illustrates well the changes associated with sc compared with iv administration. As a result of the absorption phase, the C_{max} of ertapenem is delayed and its value is lowered. A more sustained plasma concentration is obtained with sc versus iv administration.

Results of the Monte Carlo simulation and calculation of probabilities of target attainment are shown in Figure 4. Figure 5 provides the mean simulated values of $fT_{>MIC}$ as a function of MIC and dosage regimen, which may be informative for one targeting a value different from 40%. The results show that renal function influenced PTA, with higher rates of PTA in patients with moderate renal impairment compared with patients with normal renal function, as a consequence of reduced ertapenem plasma clearance. In patients with severe renal impairment, PTA values were slightly higher than in patients with moderate renal impairment (data not shown), without major differences in the profile as shown in Figure 4. The dosing regimen greatly influenced the value of the PD objective. For both the iv and sc routes, twice-daily administration of 1 g of ertapenem provided the highest PTA, all things being equal. The

recommended dosage of 1 g q24h resulted in the lowest PTA, whereas the 2 g q24h regimen's effect was intermediate. The PTA also varied with the route of administration, although to a lesser extent. Overall, the sc route was associated with higher PTA values than the iv route. The influence of dosage and route was significant for an MIC value of 1: the 1 g q24h iv regimen failed to achieve 90% PTA in patients with normal or impaired renal function, whereas 1 g q24h sc as well as all the other tested regimens achieved this goal.

Discussion

BJIs are associated with significant morbidity, mortality and a rising economic burden.[21–23] They require complex treatment strategies, including surgical procedures for most prosthetic infections, and prolonged antimicrobial therapy. When it is possible, outpatient management with parenteral antibiotic therapy is preferred to hospitalization, as it reduces the risk of hospital-acquired infection, decreases healthcare costs and improves the patient's quality of life.[24] In such an outpatient setting, sc administration of antibiotics is appealing. Compared with iv, sc administration may prove a safer, more convenient and less expensive alternative through avoiding the need for vascular access and the use and surveillance of venous catheters. There is a growing interest in sc administration of antibiotics, as illustrated by a recent study performed with ceftriaxone.[25]

Table 2. Population pharmacokinetic parameters of ertapenem

Parameter	Mean	Interindividual coefficient of variation (%)	Median (95% CI)[a]	Interindividual variance (95% CI)[a]
Subcutaneous absorption rate constant (*Ka*, h^{-1})	0.763	43.8	0.74 (0.54–0.97)	0.20 (0.070–0.40)
Non-renal clearance (CL_{NR}, L/h)[b]	1.088	58.5	1.09 (0.76–1.42)	0.38 (0.091–0.86)
Coefficient of renal clearance (CL_S, L/h per unit of CL_{CR})[b]	0.055	91.9	0.027 (0.018–0.12)	0.015 (0.0039–0.035)
Half-life (h)[c]	7.8	65.1	6.3	25.7
Apparent central volume of distribution (*Vd*, L)	6.091	31.1	6.37 (4.27–7.51)	1.14 (0.30–2.05)
Rate constant of transfer from central to peripheral compartment (K_{cp}, h^{-1})	0.292	73.1	0.49 (0.19–0.95)	0.29 (0.00020–0.42)
Rate constant of transfer from peripheral to central compartment (K_{pc}, h^{-1})	0.522	69.4	0.21 (0.16–0.36)	0.068 (0.028–0.22)
Residual error parameter λ (mg/L)	5.07	NA	NA	NA

NA, not available.
[a]The median and variance are actually weighted median and median absolute weighted deviation from the median, respectively. These values, as well as their confidence intervals, were calculated in Pmetrics by Monte Carlo simulation based on the population weighted marginal non-parametric distribution of each parameter. They correspond to the mean, variance and corresponding confidence intervals of a sample from a normal distribution.
[b]The relationship between ertapenem total body clearance (CL, in L/h), CL_S, CL_{NR} and CL_{CR} (in mL/min) is as follows: $CL = CL_{NR} + CL_S \cdot (CL_{CR} \times 0.06)$.
[c]Values for half-life were not estimated by the population algorithm but derived from the individual Bayesian posterior parameters of the 31 subjects with their initial CL_{CR}. 95% CI for median and variance are not available for this parameter.

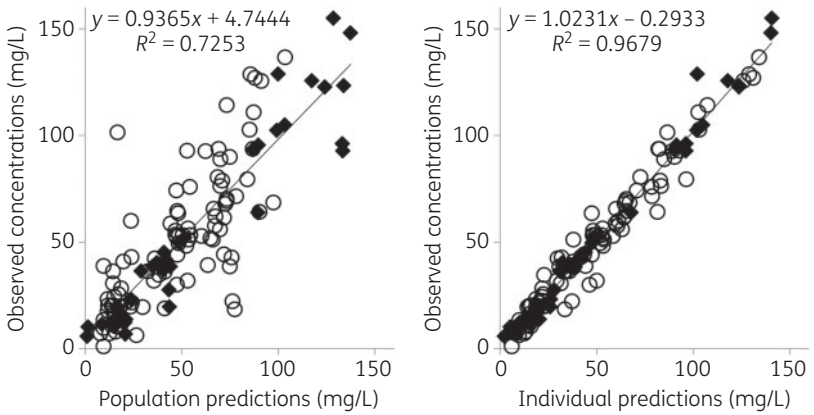

Figure 1. Goodness of fit of the final pharmacokinetic model. Observed ertapenem concentrations versus population predictions (left) and individual predictions (right). Circles, subcutaneous administration; filled diamonds, intravenous administration. The solid line is the regression line. For population predictions, bias and imprecision were −1.56 mg/L and 41.1%, respectively. For individual predictions, bias and imprecision were −0.88 mg/L and 17.8%, respectively.

Ertapenem may be used for the treatment of Gram-negative BJIs, and preliminary data have shown that sc administration appears to be safe and effective.[12] However, there is a lack of pharmacological data supporting such an administration procedure. We used a population approach to analyse PK data collected in subjects with BJI treated with ertapenem by the iv and sc routes and PK/PD simulation to examine the influence of ertapenem dosage and route of administration on PD target attainment.

The final model was a two-compartment model, with renal function influencing ertapenem plasma clearance. This is in agreement with previous PK knowledge of the drug, which is mainly cleared by the kidneys.[13,18]

PK/PD simulations performed with the final model provided important insights. First, the probability of achieving an optimal value of $fT_{>MIC}$ depended on renal function. Compared with patients with normal renal function, patients with renal impairment may have a greater probability of success, as a result of reduced ertapenem clearance. Although patients with augmented renal clearance were not specifically examined in simulations, one can expect values of $fT_{>MIC}$ and PTA to be lower than in patients with normal renal function (CL_{CR} 100 mL/min). Simulations also clarified the implication of using the sc route in terms of PD. Subcutaneous administration does not appear to decrease the value of $fT_{>MIC}$ and PTA of ertapenem compared with iv administration. In fact, it was associated with slightly higher values of $fT_{>MIC}$ for MICs ranging from 0.5 to 2 mg/L (Figure 5). This is owing to the prolongation of the drug action, as shown in Figure 3. Simulations also indicated that twice daily administration of ertapenem (either iv or sc) is associated with higher values of $fT_{>MIC}$ and PTA than the recommended dosage of 1 g q24h or a double dose of 2 g q24h. Whereas the recommended dosage of 1 g q24h by the iv route may be sufficient for MIC values <1 mg/L, 1 g q12h appears to be a more effective dosage in case of MIC values ≥1 mg/L. This is the MIC breakpoint value for resistance of anaerobic organisms such as *Bacteroides fragilis*,[13] although a small proportion of strains of common pathogens have an ertapenem MIC >1 mg/L.[26] While the safety of ertapenem at 1 g q12h has not been thoroughly evaluated, adverse drug reactions associated with ertapenem do not appear to depend on dose or drug exposure. Doses up to 3 g once daily have been administered in humans with no report of major safety issues.[27]

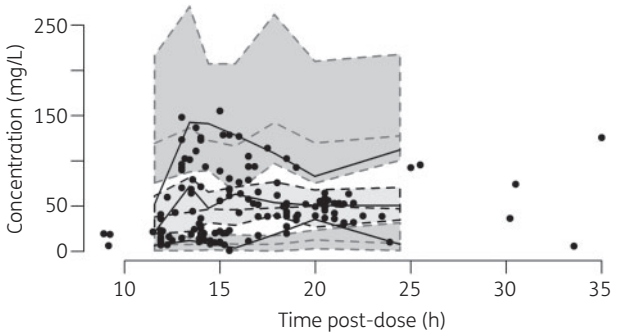

Figure 2. VPC obtained with the final model. The black dots are measured ertapenem concentrations. The solid black lines represent the 5th, 50th and 95th percentiles of observations. The grey areas show the 90% prediction interval of the 5th, 50th and 95th percentiles of predictions, these being represented by the dashed lines inside these areas.

Of note, this study has some limitations. The data were collected in routine clinical conditions and retrospectively analysed in a limited number of patients with BJI. A larger study would be necessary to confirm our findings. Second, our PK/PD simulations were based on several assumptions. We hypothesized a constant plasma protein binding of ertapenem of 5%. Protein binding of ertapenem may vary in special populations, such as critically ill patients.[28] In addition, it has been shown that the binding of ertapenem to protein was actually concentration-dependent, with a reduction from approximately 95% at plasma concentrations ~50 mg/L to about 92% at a concentration of 150 mg/L.[29] This results in a slightly less than dose-proportional increase in the drug exposure. However, the effect of this non-linear PK behaviour on drug concentrations appears to be limited.

We could not estimate intra-individual PK variability. As the model adequately fitted the data without this variability, it appears to be of limited magnitude.

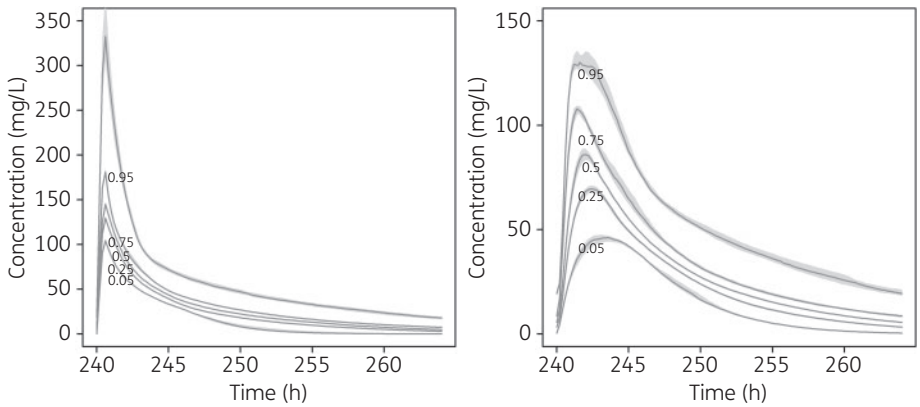

Figure 3. Model-based simulated PK profiles of ertapenem administered at 1 g q24h iv (left panel) and sc (right panel). The five profiles in each panel represent the 5th, 25th, 50th, 75th and 95th quantiles of simulated concentrations in 1000 subjects with normal renal function (CL_{CR} 100 mL/min). The grey areas represent 95% CIs around simulated quantiles. The figure shows the concentration profiles after 10 days (240 h) of therapy. Please note that different *y*-axis scales are used.

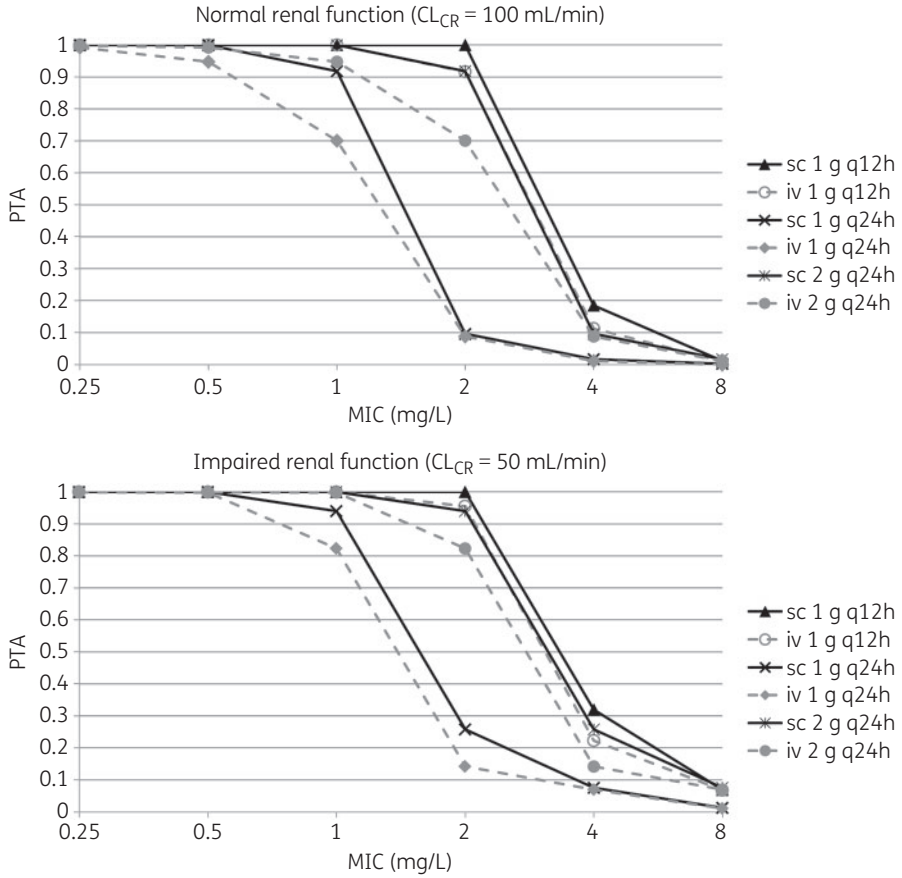

Figure 4. Probability of achieving $fT_{>MIC}$ ≥40% at the steady-state as a function of ertapenem dosing and MIC in patients with normal (upper panel) and moderately impaired (lower panel) renal function.

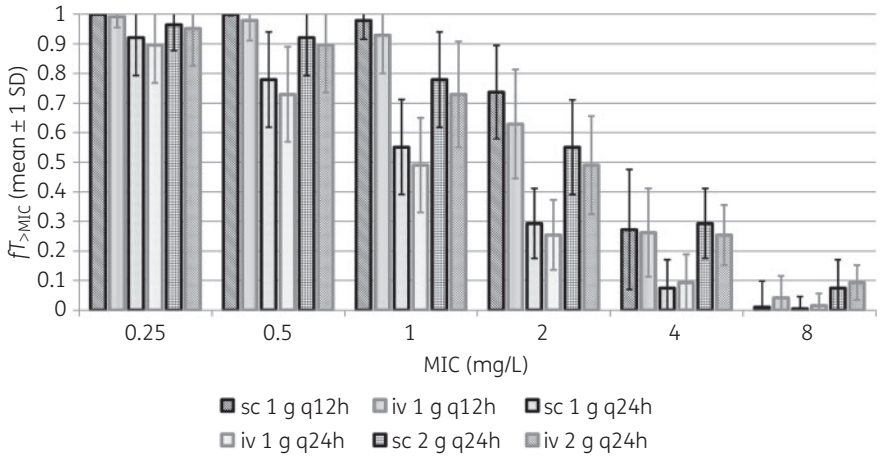

Figure 5. Value of ertapenem pharmacodynamic objective as a function of dosing regimen and MIC in patients with normal renal function. Each column symbol indicates the mean value of fractional $fT_{>MIC}$ from a simulation of 1000 patients with normal renal function (CL_{CR} 100 mL/min). The error bar on each column indicates ±1 standard deviation. Please note, as the maximal value of $fT_{>MIC}$ is 1, values of error bars >1 are not shown, as this is an artefact. For low MIC values, the distribution of $fT_{>MIC}$ is left skewed and the variability is not symmetrical around the mean.

We considered a general target for ertapenem efficacy in our PK/PD simulations, i.e. $fT_{>MIC}$ ≥40%. This target value was derived from the murine neutropenic thigh infection model and was associated with near maximal killing.[30] We assumed that such a target would apply for patients with BJI, but to our knowledge there are no data confirming the clinical relevance of this PK/PD target. Using free drug concentrations in PK/PD targets is based on the principle that only the free drug will reach the infected site by

passive diffusion and will be responsible for the antibacterial effect *in situ*. Boselli *et al.*[3] reported median tissue (in μg/g) over total serum concentration (in μg/mL) ratios of ertapenem of 0.19, 0.13 and 0.41 in cancellous bone, cortical bone and synovial tissue, respectively. These results suggest that a fraction of ertapenem total plasma concentration greater than the unbound fraction may diffuse into bones and joints. However, the interpretation of such tissue concentrations is challenging and the comparability with serum concentration is uncertain, as bone and joint are not liquid, uniform matrices.[31]

To summarize, we present the first population PK/PD analysis of ertapenem in patients with BJI treated by the iv or sc route. Compared with iv, sc administration results in lower peak concentration but prolongation of ertapenem action, with slightly higher values of time spent above the MIC. Our results suggest that twice daily administration of 1 g of ertapenem by the iv or sc route would be optimal in terms of PD target attainment in patients with BJI.

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