Pharmacokinetics of Ertapenem Administered by Intravenous or Subcutaneous Route in Patients with Bone and Joint Infections: Population and Monte Carlo simulation study

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AIM

Ertapenem is a therapeutic option in patients with difficult to treat bone and joint infections (BJI). The subcutaneous (SC) route of administration is convenient in ambulatory care setting and has shown favorable pharmacokinetic (PK) profile and tolerance [1,2]. However few PK data supporting the use of ertapenem subcutaneously are available.

METHODS

This was a retrospective analysis of data collected in patients with BJI who received ertapemem administered as a SC or intravenous (IV) 30-min infusion, from August 2010 to March 2014. An ertapenem plasma concentration profile was determined on at least one occasion in each patient, and typically included trough, peak, and 6h post-dose levels measured by HPLC.

Population PK analysis was performed by using the NPAG algorithm implemented in the Pmetrics program [3].

Then, 1000-patient Monte Carlo simulations were performed based on the final model to investigate the influence of ertapenem route of administration (SC or IV), dosage (1 g once or twice daily), and renal function on the probability of target attainment (PTA). We considered an efficacy target defined as a percentage of time during which ertapemen free plasma concentration remain above the MIC (*f*T>MIC) of 40%, assuming a protein binding of 95% [4].

RESULTS

Characteristics of the study population are shown in Table 1.

A two-compartment model, with linear SC absorption and linear elimination fit the data very well, as shown in Figure 1. Creatinine clearance (ClCr) was found to significantly influence ertapenem plasma clearance. Model parameters are shown in Table 2.

Simulations results are displayed in Figures 2 and 3. They showed that twice daily dosing, SC administration and renal impairment were associated with increased in fT>MIC and higher PTA.

Table 1. Patients' characteristics

Number of women/men	10/21
Age (years)[a]	58 (19 - 87)
Body weight (kg)[a]	75 (50 – 136)
Creatinine clearance (Cockcroft-Gault equation, ml/min)[a]	127 (54 – 237)
Glomerular filtration rate (MDRD equation, ml/min/1.73m^2)[a]	116 (56 – 218)
Ertapenem dosing regimen	SC / q12 h, n = 13; SC / q24 h, n = 7 IV / q12 h, n = 9; IV / q24 h, n = 1 IV / q36 h, n = 1
Total number of measured ertapenem concentrations	133
Total number of PK profiles per route	SC, n = 33; IV, n = 13
Number of measured ertapenem concentrations per subject	3 (1 – 12)

Except where indicated by numbers, data are given as median (min-max)

[a] Values recorded on the first TDM occasion

RESULTS (continued)

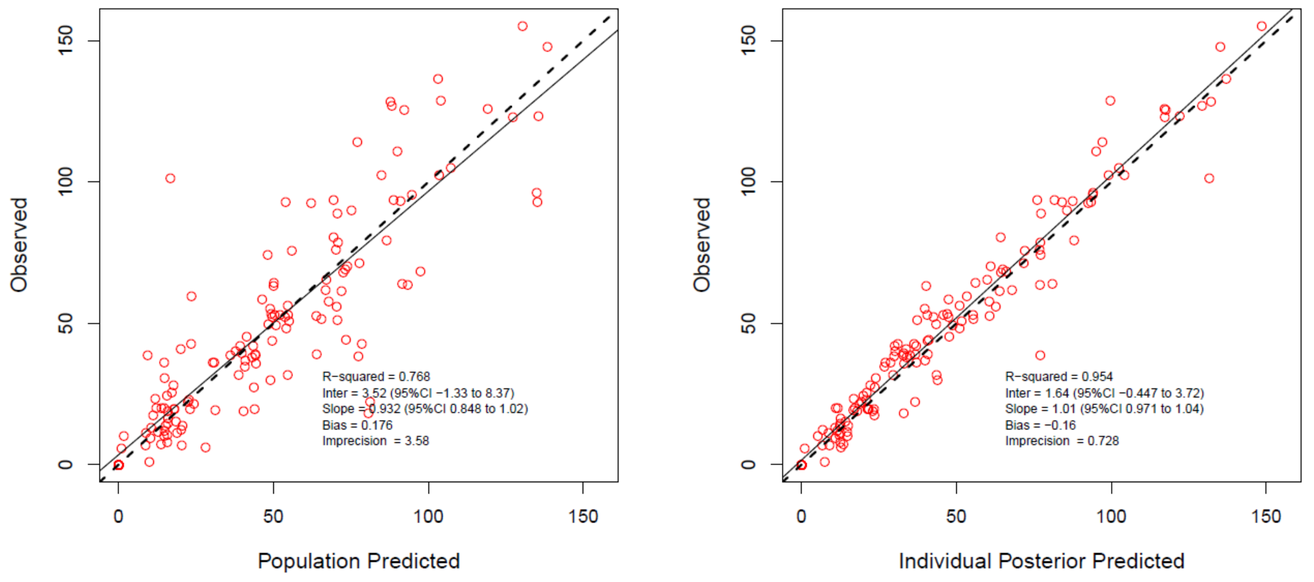


Figure 1. Observed ertapenem concentration versus model-based population (left panel) and individual (right panel) predictions.

Table 2. Population PK parameters of ertapenem estimated by the NPAG algorithm

Parameter	Mean	Coefficient of variation (%)
Subcutaneous absorption rate constant (Ka, h^{-1})	0.763	43.8
Non-renal clearance (Cl_{NR}, L/h)	1.088	58.5
Coefficient of renal clearance (Cl_S, L/h per unit of ClCr)	0.055	91.9
Apparent central volume of distribution (Vd, L)	6.091	31.1
Rate constant of transfer from central to peripheral compartment (Kcp, h^{-1})	0.292	73.1
Rate constant of transfer from peripheral to central compartment (Kpc, h^{-1})	0.522	69.4

Figure 2. Probability of achieving ertapenem free T>MIC > 40% in patients with normal (ClCr = 100 ml/min, left panel), and impaired (ClCr = 50 ml/min, right panel) renal function

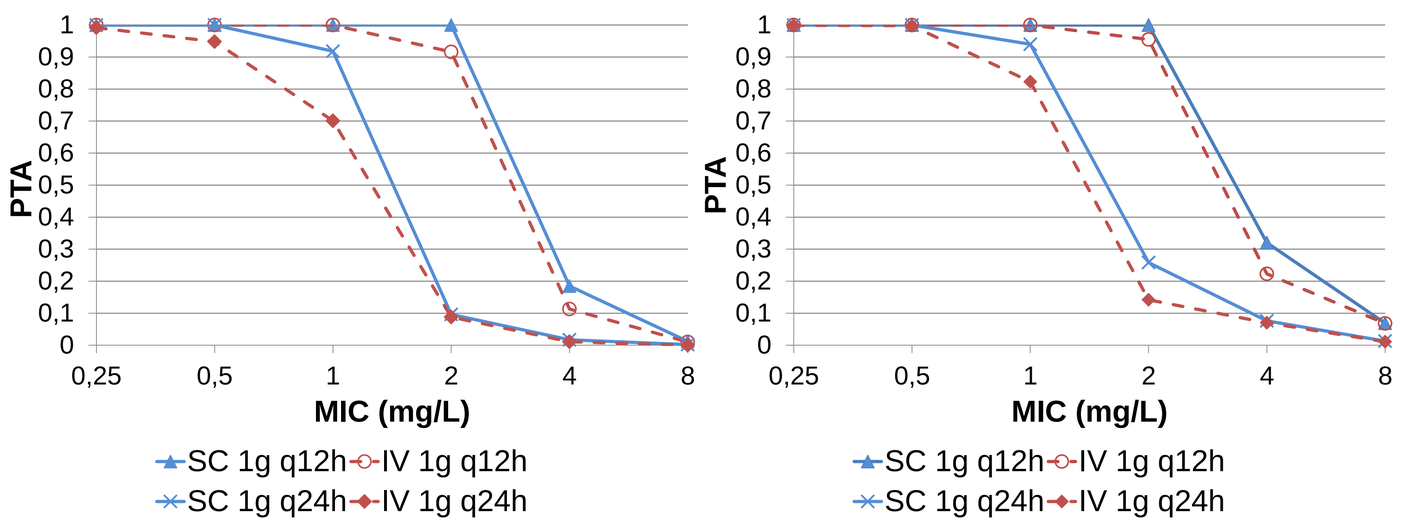
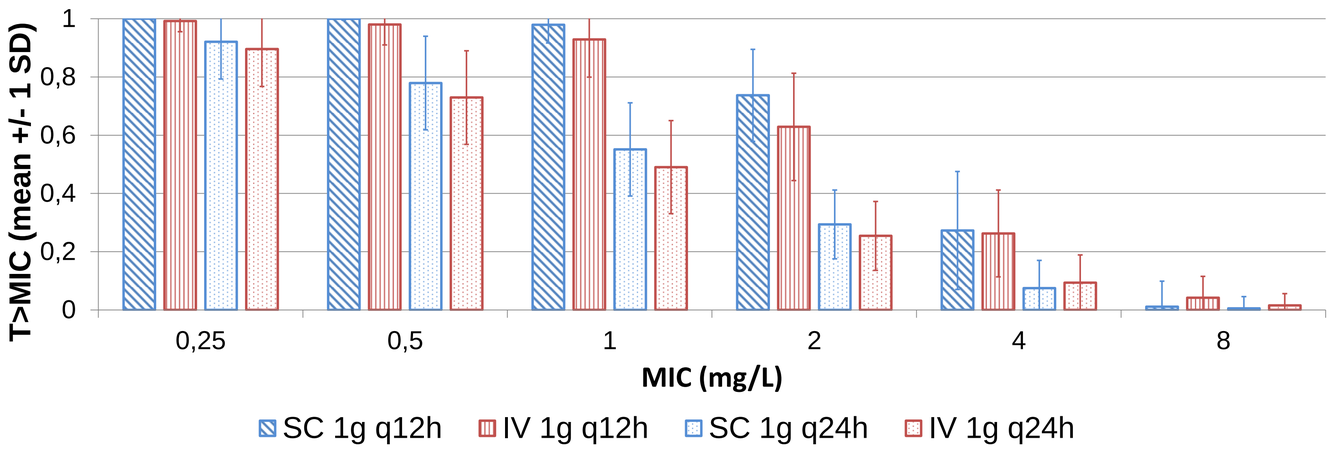


Figure 3. Predicted percentage of time spent above the MIC during a dosing interval (T>MIC) in patients with normal renal function



CONCLUSION

This is the first population pharmacokinetic study of ertapenem in patients with BJI and the first population model for the SC route of administration. The results suggest that 1 g administered twice daily, subcutaneously may optimize ertapemem exposure in patients with BJI.

References: [1] Frasca *et al.* Antimicrob Agents Chemother. 2010 Feb;54(2):924-6; [2] Ferry *et al.* J Infect. 2012 Dec;65(6):579-82, [3] Neely *et al.* Ther Drug Monit. 2012 Aug;34(4):467-76, [4] Chen *et al.* Antimicrob Agents Chemother 2006 Apr;50(4):1222-7

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