High Doses of Ertapenem (1g/12h) Administered Subcutaneously Optimize Ertapemem Exposure in Patients with Bone and Joint infections (BJI): a Monte Carlo Simulation Study

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Background

Ertapenem (ERT) could be used for the treatement of BJI, but high doses (1g/12h) seem to be more appropriate that the standard dose of 1g/day. The subcutaneous (SC) route of administration is convenient in ambulatory care setting but, to date, no pharmacokinetic (PK) data supporting the use of high doses of ERT subcutaneously are available

Methods

This was a retrospective analysis of data collected in patients with BJI who received ERT (1g/ day or 1g/12h) administered as a SC or intravenous (IV) 30-min infusion, from August 2010 to March 2014. An ERT plasma concentration profile was determined on at least one occasion in each patient, and typically included trough, peak, and 6h post-dose HPLC-measured levels.

Population PK analysis was performed by using the NPAG algorithm implemented in Pmetrics [1]. Then, 1000-patient Monte Carlo simulations were performed based on the final model to investigate the influence of ERT route of administration (SC or IV), dosage (1g 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 ERT free plasma concentration remain above the MIC (*f*T>MIC) of 40%, assuming a protein binding of 95% [2].

[1] Neely et al. Ther Drug Monit. 2012;34(4):467-76, [2] Chen et al. Antimicrob Agents Chemother 2006;50(4):1222-7

Results

Characteristics of the study population are shown in **Table 1**. A two-compartment model, with linear SC absorption and 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**.

Table 1. Patients' characteristics

Number of women/men	10/21
Age (years)[a]	58 (19 - 87)
Body weight (kg)[a]	75 (50 – 136)
ClCr (Cockcroft-Gault equation, ml/min)[a]	127 (54 – 237)
GFR (MDRD equation, ml/min/1.73m^2)[a]	116 (56 – 218)
ERT 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 PK profiles	SC, n = 33; IV, n = 13
Measured ERT concentrations	Total, 133 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

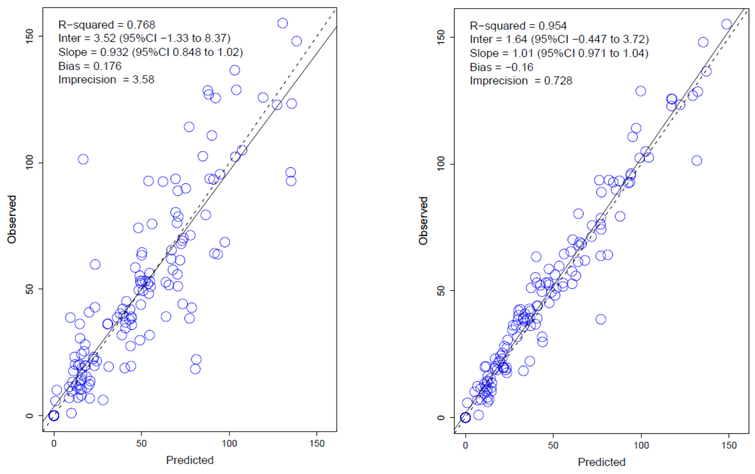


Figure 1. Observed ERT concentration versus model-based population (left panel) and individual (right panel) predictions.

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 *f*T>MIC and higher PTA.

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

Parameter	Mean	CV(%)
Subcutaneous Ka, (h^{-1})	0.763	43.8
Cl_{NR}, L/h	1.088	58.5
Cl_S, (L/h per unit of ClCr)	0.055	91.9
Vd (L)	6.091	31.1
K12 (h^{-1})	0.292	73.1
K21 (h^{-1})	0.522	69.4

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

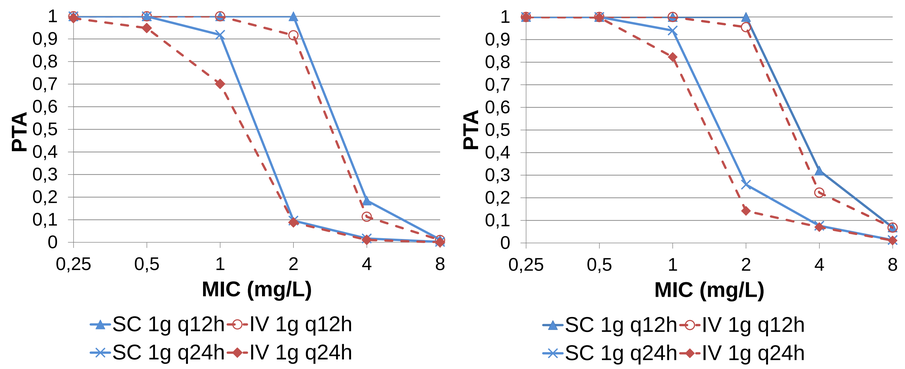
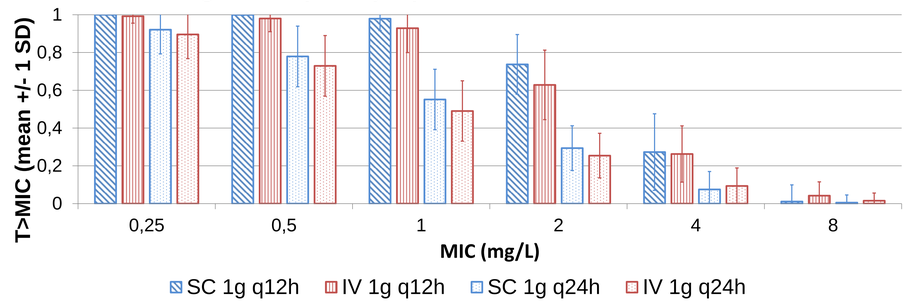


Figure 3. Predicted percentage of time spent above the MIC during a dosing interval (T>MIC) in patients with normal renal function



Conclusion

Our study suggests that the subcutaneous administration of ERT at the dose of 1g/12h may optimize drug exposure in patients with BJI.

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