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Pharmacodynamic profiling of prolonged infusion of Ertapenem in critically ill patients with early onset ventilator associated pneumonia through the use of a population pharmacokinetic model and Monte Carlo simulation

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ABSTRACT

Objectives: Ertapenem (ERT) is a broad spectrum carbapenem antibiotic with nonlinear protein binding characteristics best described by a two class binding site model. The objective of this study was to describe the effects of prolonging the infusion or changing frequency of administration on the Probability of Target Attainment (PTA) of ERT at doubling MIC dilutions in critically ill patients with early onset ventilator associated pneumonia (VAP).

Methods: Pharmacokinetic (n=17) data for ERT in critically ill patients with early onset VAP was used in this analysis. Free ERT concentrations were calculated with the two class binding site model using measured albumin concentrations for the specific and remaining protein concentrations for the non-specific binding site. Standard dose of 1g ERT was evaluated for PTA with Monte Carlo simulation (MCS, n=5000) using 0.5, 1, 2, 3, and 4 hour infusion times at the MIC ranges of 0.0625 to 4 mg/L at bacteriostatic (20%) and bactericidal (40%) fT>MIC targets. Additionally, 0.5 g at 12 h interval infused over 0.5 h was modeled to evaluate for the impact of more frequent administration on attaining the desired pharmacodynamic target.

Results: Standard dose of 1g ERT PTAs to achieve bacteriostatic effects were more than 90% up to an MIC of 0.5 mg/L for all regimens, while the PTA decreased below 80% at the MICs of 1 mg/L or more. All infusion strategies showed over 80% PTA up to the MIC of 0.25 mg/L for bactericidal targets, with an increase of nearly 3 % by each hour added to the infusion time. At the MICs of 0.5 ug/ml or higher, the PTA was less than 80% for standard and prolonged infusions, with an increase of nearly 4 % by each hour added to the infusion time. Interestingly, when the total daily dose of 1 g was divided into equal 0.5 g doses and given at 12 h intervals over 0.5 h, greatly improved (14% or more) PTAs were showed over the range of MICs for the bactericidal target.

Conclusion: We conclude that prolonging the infusion of ERT would have minimal effects on the PTA. Instead, more frequent administration or giving the total daily dose in divided doses at more frequent intervals should be considered to optimize the pharmacodynamics of the highly protein bound ERT.

INTRODUCTION

ERT is a carbapenem antibiotic with activity against clinically relevant gram-negative organisms. It is FDA approved for the treatment of complicated intra-abdominal infections, complicated skin and skin structure infections, community acquired pneumonia, acute pelvic infections, and complicated urinary tract infections, including pyelonephritis[1]. In clinical practice, ERT is typically used for the treatment of serious gram-negative infections at doses that range from 0.5g to 1g every 24 hours as a 30 min infusion. The pharmacokinetic profile of ERT has been well described in healthy volunteers, obese individuals, and in some critically ill patient populations[2,3]. It is well established that β-lactam antibiotics such as ERT kill bacteria best when their concentrations are maintained above their MIC for a specific percentage of the dosing interval.[4] Studies in animal models of infection have shown that the *f*T>MIC was critical in predicting ERT efficacy. Murine infection models have confirmed these observations for ERT identifying close to 40% *f*T>MIC as the maximum bactericidal exposure during 24 hour experiments, and near 20% *f*T>MIC to achieve the state of bacteriostasis.[5] With a well defined pharmacodynamic target and population pharmacokinetic model, we are able to design ERT dosing regimens that have the highest probability of obtaining these endpoints over a range of MICs by using a computer simulation platform called Monte Carlo simulation. This compound with a non-linear, highly protein bound nature in healthy adults with normal kidney function at its standard dosing regimen of 1g every 24 hours infused over 0.5 hour may results in a suboptimal probability of achieving 40% *f*T>MIC for bacteria with MICs ≥0.25 µg/ml.[6] Methods to improve target attainment rates for time dependent antibiotics are well documented in previous reports.[7] The two techniques most likely to result in superior pharmacodynamics are the prolongation of infusion times or the increased frequency of drug administration. In this report, we evaluate the impact of prolonging the infusion time and increasing the dosing frequency on the PTA of ERT in critically ill patients with early onset VAP.

METHODS

Monte Carlo Simulation

- 5000 trial Monte Carlo Simulation (Crystal Ball Fusion Edition,v.11.1.2.1.000; Oracle Corp. Redwood Shores, CA, USA)
  - Previously published popPK model derived from concentration – time data of 17 patients with early - onset VAP was used in this analysis[3]
  - Two compartment model best fit the data characterized by clearance (CL), volume of distribution of the central compartment (V_c), intercompartmental clearance (Q), and volume of distribution of the peripheral compartment (V_p)
  - Creatinine clearance was identified as a significant covariate on CL in the model
  - Free drug concentrations were calculated using the two-class binding site equation (Eq. 1.), where C_b is the bound concentration, C_f is the free concentration, n_1 and n_2 are the number of binding sites, k_1 and k_2 are the association rate constants for the binding sites, and p_1 and p_2 are the concentrations of albumin and remaining plasma protein:

$$\text{Eq. 1.} \qquad C_b = [(n_1 * p_1 * k_1 * C_f) / (1 + k_1 * C_f)] + n_2 * p_2 * k_2 * C_f$$

  - A model with constant input and first order output was used to estimate free concentration – time profiles for each simulated patient at steady state
  - All model parameters were assumed to follow lognormal distribution
- Pharmacodynamic target
  - PK/PD Index of the fT>MIC necessary to achieve bacteriostatic (20%) and bactericidal (40%) activities were utilized as the goal of evaluation
- Dosing strategies
  - Standard 1g dose of ERT was evaluated at 0.5, 1, 2, 3, and 4 hour infusion times at the MIC ranges of 0.0625 to 4 mg/L
  - Additionally, 0.5 g at 12 h interval infused over 0.5 h was modeled to evaluate for the impact of more frequent administration on attaining the desired pharmacodynamic target.

RESULTS

	Simulated Pharmacokinetic Parameters			
	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)
Mean	2.48	11.38	4.13	0.84
Median	2.27	11.07	3.8	0.81
SD	1.09	2.63	1.84	0.24

Table 1. Summary statistics of simulated ERT pharmacokinetic parameters

Dosing Regimen	MIC (mg/L)						
	0.0625	0.125	0.25	0.5	1	2	4
	Bacteriostatic Probabilities of Target Attainment						
1g q24h 0.5h infusion	1.00	1.00	0.98	0.91	0.64	0.19	0.00
1g q24h 1h infusion	1.00	1.00	0.99	0.93	0.69	0.21	0.01
1g q24h 2h infusion	1.00	1.00	0.99	0.96	0.74	0.22	0.01
1g q24h 3h infusion	1.00	1.00	1.00	0.98	0.76	0.23	0.01
1g q24h 4h infusion	1.00	1.00	1.00	0.99	0.79	0.23	0.00
0.5g q12h 0.5h infusion	1.00	1.00	1.00	0.97	0.67	0.12	0.00
	Bactericidal Probabilities of Target Attainment						
1g q24h 0.5h infusion	0.98	0.93	0.81	0.54	0.21	0.02	0.00
1g q24h 1h infusion	0.99	0.94	0.82	0.57	0.22	0.02	0.00
1g q24h 2h infusion	0.99	0.95	0.84	0.61	0.25	0.03	0.00
1g q24h 3h infusion	0.99	0.96	0.87	0.65	0.27	0.04	0.00
1g q24h 4h infusion	0.99	0.97	0.90	0.69	0.29	0.03	0.00
0.5g q12h 0.5h infusion	1.00	0.99	0.94	0.73	0.30	0.03	0.00

Table 2. Probabilities of target attainment for evaluated ERT dosing regimens

RESULTS

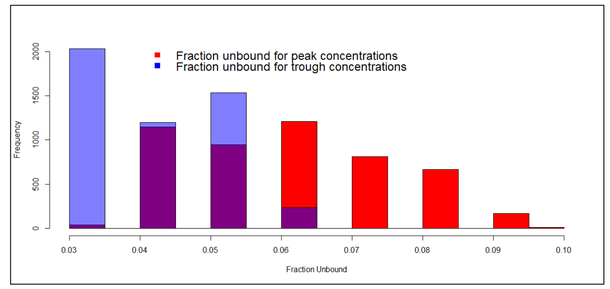

Figure 1. Histograms of unbound fraction for ERT peak and trough concentrations

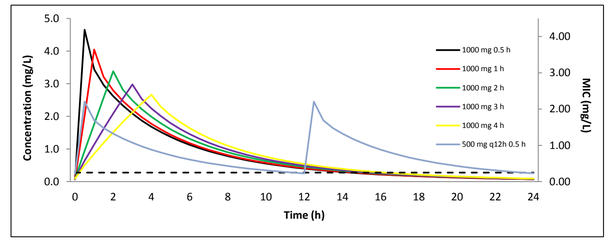

Figure 2. Free median population-predicted concentration-time profiles for ERT regimens

CONCLUSION

- Based on this experiment, extending the infusion times from 0.5 to 4 hours at 1 hour increments resulted in a modest increase of the PTAs for the 1g every 24 hour regimens. Each hour added to the infusion time increased PTAs by 1 to 4% at the specific MICs for the bactericidal targets. Only the 4 hours infusion time resulted in the PTA at least 90% at the MIC of 0.25 mg/L, while none of the regimens showed optimal PTA at the MIC of 0.5 mg/L, the current susceptibility breakpoint referenced by the EUCAST and the CLSI for ERT against *Enterobacteriacea*.
- Increased frequency of drug administration is the second alternative to improve PTAs of time dependent antibiotics. Splitting the 1g dose every 24 hours infused over 0.5 hours into 0.5g doses given every 12 hours over 0.5 hour resulted in markedly higher increase in the rates of PTAs. Depending on the MICs, a rise of up to 19% was observed with this regimen as compared to the 1g dose given over 0.5 hours, a magnitude that was not observed with the prolonged infusion strategies. Therefore, more frequent administration or giving the total daily dose in divided doses at more frequent intervals should be considered to optimize the pharmacodynamics of the highly protein bound ERT.

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