Title: Population Pharmacokinetic (PK) Pharmacodynamic (PD) Evaluation of Eritoran tetradsodium (E5564) in Patients with Severe Sepsis

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Objectives: Eritoran is a synthetic analogue of the Lipid A portion of the lipopolysaccharide (endotoxin) molecule and an antagonist of TLR4 (toll-like receptor 4). Eritoran suppresses endotoxin-induced TNF production and is being investigated for treatment of patients with severe sepsis (SPAT). The objective was to develop a population PK / PD (mortality) model for eritoran in SPATs.

Methods: Eritoran concentrations were from a double blind randomized placebo controlled study in ICUs. Approximately 100 SPATs each who met study enrollment criteria each received placebo, 45 mg or 105 mg eritoran IV divided over 6 days, doses given every 12h. Sparse sampling involved taking samples at 3 of the following times: For dosing-interval (DI) 1: pre-dose (0 hr), 4 and 8 hours after start of infusion. For the next 9 DIs: 0, 4 and 7 hours after start of infusion. For final DI: 0, 7, 12 hr, and 2, 4, 6 and 8 days after start of infusion. Eritoran concentrations were used for PK modeling. Exposure was correlated with survival using binomial logistic regression. Data were analyzed using NONMEM V Level 1.1.

Results: PK was described using a linear two compartment model. Clearance (CL) was estimated as $CL=0.11*(IL6/10)^{0.061}*(HDL/80)^{-0.209}*(BSA/1.8)^{0.87}$, central volume ($V_1$) as $V_1=3.65*(BSA/1.8)^{1.02}$, inter-compartmental clearance ($Q$) as $Q=0.0357$ L/h and peripheral volume ($V_2$) as $V_2=1.73$ L. After including covariates in the model, inter-individual variability reduced from 56% to 46% and from 39% to 36.6% for CL and $V_1$, respectively. The final PD model was a logistic regression model where baseline age, APACHE II Score, PROM Score and IL6 were identified as covariates. The PD model based $C_{ss,avg}$ showed a trend that correlated with higher rate of survival but did not reach statistical significance. As an example using this PD model, we can estimate that a patient (age=25 years, PROM=40, IL6=500, APACHE=30) has a survival probability of 55% if untreated and 74% with a $C_{ss,ave}=10,000$ ng/ml (corresponding to 105 mg of eritoran).

Conclusions: Eritoran PK is well described by the linear two compartment model. This PK / PD model, incorporating four covariates (age, PROM, IL6, APACHE), may predict survival rates based on $C_{ss,ave}$.

References:


