%T>MIC Predicts Probability of Microbiological Outcome in the Treatment of Nosocomial Pneumonia by Ceftobiprole

Anouk E. Muller1,2, Nieko Punt3 and Johan W. Mouton1

1 Radboud University Nijmegen Medical Centre, NL; 2 Elisabeth Hospital, Tilburg, NL; 3 Medimatics, Maastricht, NL

Introduction

Ceftobiprole (BPR) is a novel cephalosporin with bactericidal activity against Gram-negative (GN) and Gram-positive bacteria, including MRSA and P. aeruginosa. A randomized, double-blind phase 3 clinical trial (NCT00210964; BAP549307) was conducted comparing the efficacy of BPR (500mg tid 2h infusion) with ceftazidim (2g tid 2h infusion plus intravenous 600mg tid 1h infusion) in patients with nosocomial pneumonia (NP). We explored the relationship of BPR exposure and microbiological outcome (MO). For microbiological outcome, we looked at eradication of baseline (BL) micro-organisms as well as eradication of all micro-organisms (thus including those at end of treatment (EOT)).

Methods

Individual exposures were determined in each patient and related to microbiological outcome. The overall strategy of the analysis is shown below:

Exposure

PK data and covariates

Individual PK parameters

Culture results with MIC values

MIC values per individual

Microbiological outcomes

BL micro-organisms

BL + EOT micro-organisms

Pharmacokinetic (PK) and demographic data from patients (N=177) in 6 clinical trials including the NP study were used to construct a population PK model of BPR using NONMEM. Individual PK parameters and %T>MIC were determined for each patient using covariates and data from sparse sampling. MICs used in the analyses were the highest MICs of any pneumonia-relevant pathogens cultured at BL, or at BL and EOT. Successful treatment was defined as negative cultures of BL micro-organisms (BCEOT) or any micro-organism at EOT (CEOT), respectively. Separate analyses were performed for Gram-negative (GN) micro-organisms and all micro-organisms. CART analyses were performed using SAS JMP software. Multiple logistic regression was performed using entry criteria of 0.15 and stay criteria of 0.1 and included demographic variables as well as the infection type (Ventilator Associated Pneumonia (VAP) or non-VAP). An Emas model was used to fit response data (Graphpad Prism 5.0).

Results

A 3-compartment model best fit the data with creatinine clearance as covariate on clearance and age on the central compartment. Using the model %T>MIC was determined for 251 patients in the NP study, for some patients creatinine was not available. Figure 1 shows the overall distribution of the highest MICs of micro-organisms cultured.

CART analysis showed significant correlations between exposure and response for both eradication of GN baseline micro-organisms as well as all GNs (table 1a). Similar significant relationships were found for all micro-organisms (table 1b). All measures of exposure as well as the MIC were significant. A %T>MIC value of >62.2% (p<0.001) for all micro-organisms and a similar value if only Gram-negative pathogens were considered (%T>MIC, p<0.001) was found.

Since all measures of exposure showed significance and there was no co-linearity between exposures, a multiple logistic regression analysis was performed to determine which of the exposures was best predictive. For GN, after forward and backward procedures, only %T>MIC was significant in the model, both for eradication of BL micro-organisms as well as for BL and EOT micro-organisms.

The Emas model for %T>MIC for GN micro-organisms showed a good fit (R2 =0.37). The benefit of adequate treatment increased from an eradication rate of 0.44 at %T>MIC of 0% to 0.85 at 100%, respectively, as shown in figure 2a. The %T>MIC for GP micro-organisms was 100% in most cases due to the relatively low MICs of GP micro-organisms (results not shown).

Discussion

Pharmacokinetic data of ceftobiprole obtained from 6 clinical trials resulted in a population model with three compartments. There were only two covariates significant in the model, creatinine clearance on clearance and age on the volume of distribution. Importantly, the presence or absence of VAP was not significant as a covariate. Although VAP patients did have a slightly higher clearance, this could be fully explained by creatinine clearance. Using the population model we could determine PK/PD indices for patients with nosocomial pneumonia and a good correlation with exposure was demonstrated. We used two measures of outcome, eradication of BL micro-organisms as well as those cultured at BL and EOT. We included the latter measure because we reasoned that the effects of exposure do not only involve the micro-organisms at the start of therapy (BL) but also during treatment. The correlations found were better for the latter.

We focused on GNs because these are most relevant in patients with NP. Furthermore, MICs of most GP MO are relatively low, and relatively few patients did have a %T>MIC below 100%. In both analyses however good correlations were found with exposure.

Conclusions:

• Microbiological outcome at end-of-treatment is significantly correlated with exposure to ceftobiprole
• A high probability of microbiological eradication was attained at 62.2% %T>MIC or higher.
• The results concur with values observed in preclinical models and those of cefazidime1

1. Muller et al. ECCMID, London 2012