Ceftobiprole is a broad-spectrum cephalosporin with activity against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE). It binds to PBP2a, the main determinant of cell wall synthesis. Ceftobiprole is rapidly absorbed after oral administration, with peak plasma concentrations occurring within 1–2 hours. It has a long half-life, allowing for once-daily dosing.

Methods

Ceftobiprole pharmacokinetic (PK) data from healthy volunteers and patients in phase 1 (N=100), phase 2 (N=424), and two phase 3 (N=913) trials were combined to identify factors contributing to inter-individual variability in PK of ceftobiprole. NONMEM was used to develop a PK model with statistically significant covariates. PK modeling was performed to assess the impact of renal function on the pharmacokinetics of ceftobiprole. The model was validated using a test data set that comprised 35% of the study population from one of the phase 3 studies. The final population PK model was used to simulate the PK profile of ceftobiprole under different dosing regimens and to estimate the time above minimum inhibitory concentration (%T>MIC).

Results

The influence of age, weight, body weight, or the assessed concomitant medications on PK was negligible, with suggested dosing regimen adjustments based on degree of renal function. Exploratory analyses of sex and concomitant medications as covariates suggested no change in PK of ceftobiprole due to these factors.

Conclusions

- The external model validation of the optimized full covariate model showed that the model had good predictability, hence the parameters were re-estimated for most clinically important Gram-positive and Gram-negative pathogens, including bacteria with decreased susceptibility and resistant strains.
- Of the covariates included in the model, only the renal function was identified as a clinically relevant factor using T>MIC. Age and sex were not statistically clearly influential when creatinine clearance was included as a covariate. The influence of other potentially relevant covariates such as gender and body weight on PK was negligible, with suggested dosing regimen adjustments based on degree of renal function. Exploratory analyses with sex and concomitant medications as covariates suggested no change in PK of ceftobiprole due to these factors.

References