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Population Pharmacokinetic Analysis to Support Dosing Regimens of Ceftobiprole

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Abstract

Introduction: Ceftobiprole is a broad-spectrum cephalosporin with activity against methicillin-resistant staphylococci. Dosage adjustment strategy was supported by a population analysis approach.

Methods: Ceftobiprole plasma pharmacokinetic (PK) data from healthy volunteers and patients in eight phase 1 (n=162), one phase 2 (n=27), and two phase 3 (n=414) clinical 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. To test clinical relevance of the covariates, the percentage of time the concentrations of ceftobiprole above MIC during a dosing interval (%T>MIC) was estimated, which is the PK/PD index of ceftobiprole.

Results: A three-compartment model with first-order elimination provided the best fit for the ceftobiprole plasma-concentration time-profile. In the final population PK model, clearance (CL) was a function of creatinine clearance and health status (healthy volunteers vs patients); volume of distribution in the central compartment (V1) was a function of body weight and health status; volume of distribution in a shallow peripheral compartment (V2) was a function of gender and health status; volume of distribution in a deep peripheral compartment (V3) was a function of gender. Of these covariates, only the renal function was identified as the clinically relevant factor using %T>MIC. Age (ie, ≥18 years old) was neither statistically nor clinically influential when creatinine clearance was included as a covariate. The influence of other statistically significant 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 race and concomitant medications as covariates suggested no change in PK of ceftobiprole due to these factors.

Conclusion: The population PK analyses support the proposed labeling dosing for ceftobiprole and dosing adjustments based on creatinine clearance only. No adjustments to ceftobiprole dosing appear to be warranted for age, race, gender, body weight, or the assessed concomitant medications.

Table 1. Parameter estimates and standard errors for the final population PK model

Parameter	Population Mean		Magnitude of Between-Subject-Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
CL (L/h)[a]	5.36	1.06	20.45	19.93
V1 (L)[b]	7.40	2.96	46.48	26.06
Q2 (L/h)	11.20	6.52	na	na
V2 (L)[c]	6.10	3.43	5.99	28.13
Q3 (L/h)	0.76	6.96	na	na
V3 (L)[d]	3.27	4.10	12.17	47.91
Exponent for CLcr (normalized by 120 mL/min)	0.82	4.07	na	na
Coefficient for V2 due to health status (V2HL)	0.57	15.90	na	na
Coefficient for V3 due to sex (V3SEX)	-0.18	9.46	na	na
Coefficient for CL due to health status (CLHL)	0.20	12.16	na	na
Exponent for V1 (normalized by 75 kg, V1WT)	1.05	12.95	na	na
Coefficient for V1 due to health status (V1HL)	0.45	18.00	na	na
Coefficient for V2 due to sex (V2SEX)	-0.13	35.89	na	na
Residual variability: sparsely sampled	36.06%CV	14.08		
Residual variability: intensively sampled	13.42%CV	7.28		
BOV (CL)			28.88	20.86
BOV (V1)			8.73	23.75
Block (CL vs V1)	correlation coefficient = 0.68			

na = not applicable
[a] For a healthy volunteer with CLcr of 120 mL/min; [b] For a healthy volunteer with 75 kg body weight; [c] For a male healthy volunteer; [d] For a male subject

Introduction

- Ceftobiprole[1] is a broad-spectrum cephalosporin that binds to PBP2a, the main determinant of methicillin resistance in staphylococci.
- Ceftobiprole also possesses activity against most clinically important Gram-negative pathogens.
- Ceftobiprole 500 mg every 8 h administered as a 2-h infusion is anticipated to provide %T>MIC for most clinically important Gram-positive and Gram-negative pathogens, including bacteria with decreased susceptibility and resistant strains.[2]
- Ceftobiprole 500 mg every 12 h administered as a 1-h infusion is anticipated to provide %T>MIC for most clinically important Gram-positive pathogens.
- A population analysis approach was used to inform a dosage adjustment strategy by evaluating the influence of demographic characteristics and other covariates on ceftobiprole pharmacokinetics.

Methods

Study Population

- Ceftobiprole plasma pharmacokinetic (PK) data from a total of 603 subjects (162 healthy volunteers and 441 patients) in eight phase 1 (n=162), one phase 2 (n=27), and two phase 3 (n=414) clinical trials were combined to identify factors contributing to inter-individual variability in PK of ceftobiprole (**Table 1**).

PK Modeling

- NONMEM was used to develop a compartmental PK model to investigate the impact of statistically significant covariates on the PK parameters such as clearance, volume of distribution, and inter-compartmental flow rate of ceftobiprole.
- The NONMEM data set used to develop the final population PK model comprised 5185 pharmacokinetic samples from the study population.
- Inclusion of the covariates into a full covariate model was based primarily on graphical covariate search and complemented by generalized additive modeling analysis. Covariates were investigated using a stepwise forward selection (α=0.01) and backward elimination (α=0.005).
- An analysis of the effects of concomitantly administered drugs was based on medications that were administered to more than 10% of the study population (ie, >44 patients).
- The external model validation of the optimized full covariate model was performed using a test data set that comprised 35% of the study population from one of the phase 3 studies. The optimized full covariate model had good predictability, hence the parameters were re-estimated using the combined data set of the index and test data to estimate the final population PK parameters.

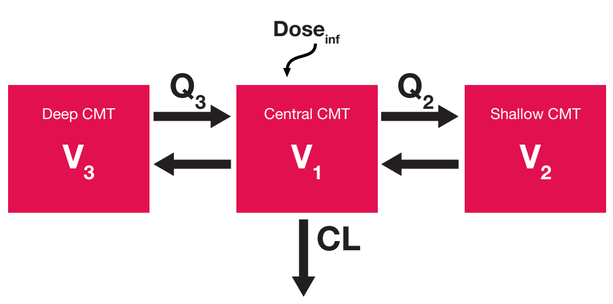
Simulation to Test the Clinical Relevance of Covariates

- The percentage of time the concentrations of ceftobiprole above MIC (4 µg/mL) during a dosing interval (%T>MIC) was calculated, as this is the PK/PD index of ceftobiprole.
- 1000 patients were simulated using the final population PK model. The dosing regimen used in the simulation was ceftobiprole 500 mg, 2-h infusion, q8h.

Results

- A three-compartment model with first-order elimination provided the best fit for the ceftobiprole plasma-concentration time-profile (**Figure 1**).

Figure 1. Three-compartment model.



Deep CMT: Deep peripheral compartment
Central CMT: Central compartment
Shallow CMT: Shallow peripheral compartment
Vn: Volume of distribution (L)
CL: Clearance rate (L/h)
Q2: Distribution clearance between shallow and central compartments (L/h)
Q3: Distribution clearance between deep and central compartments (L/h)

- The equations for computing the CL, V1, Q2, V2, Q3, and V3 of ceftobiprole from the final PK model are:

  $CLj(L/h)=5.36 * (CRCLj/120)^{0.82}*(1+0.2 * HLTHj)$

  $V1j(L)=7.40 * (WTj/75)^{**\ 0.45}*(1+1.05*HLTHj)$

  $Q2j\ (L/h)=11.20$

  $V2j(L)=6.10 * (1–0.13 * SEXj) * (1+0.57 * HLTHj)$

  $Q3(L/h)=0.76$

  $V3j(L)=3.27 * (1–0.18 * SEXj)$

where,

TVX_j = the typical value of the *X* parameter for the j^{th} subject;

WTj = the weight (kg) of the j^{th} subject (centered around a median weight of 75 kg);

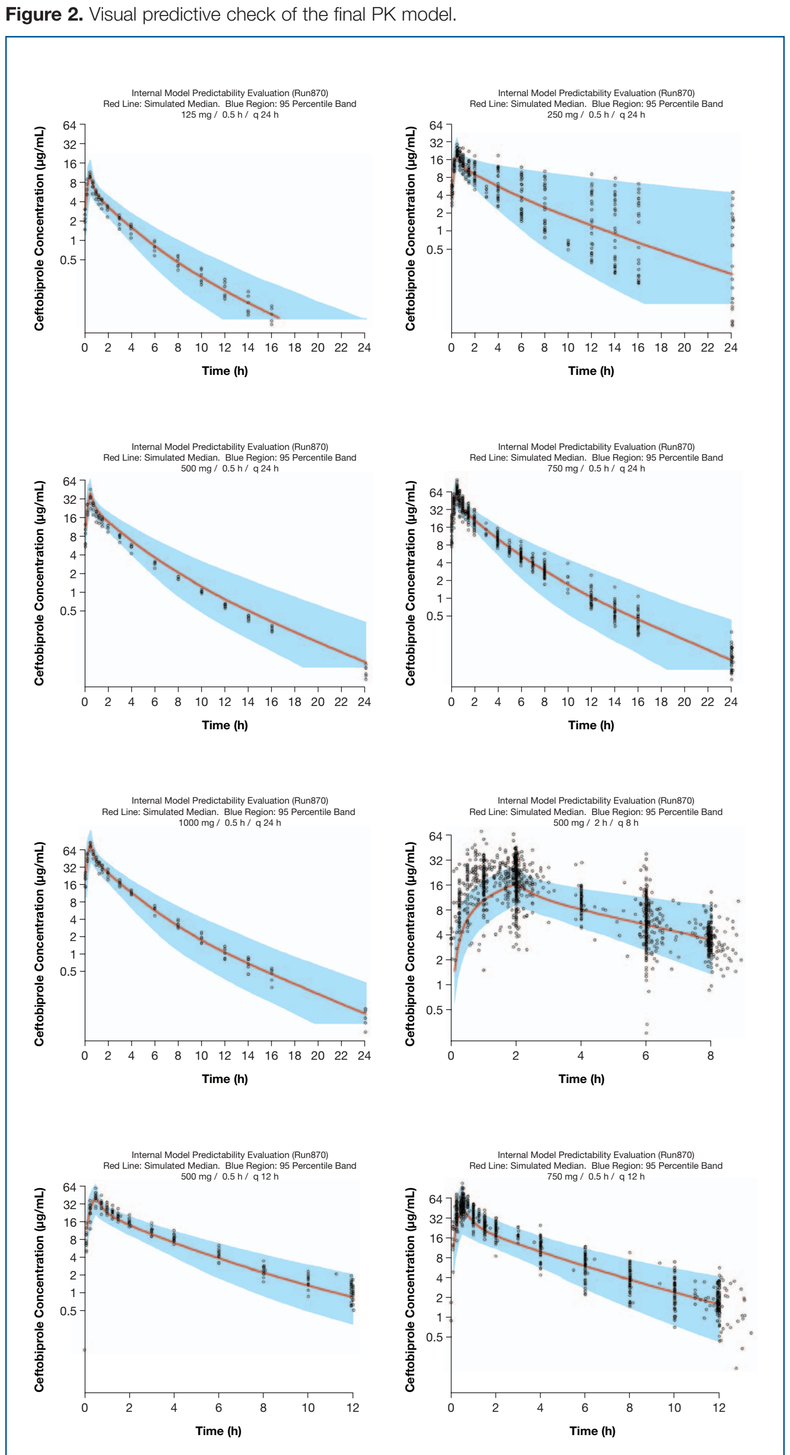
CRCLj = the creatinine clearance (mL/min) of the j^{th} subject;

HLTHj = health status indicator variable in the j^{th} subject (healthy volunteers or patients);

SEXj = sex indicator variable in the j^{th} subject

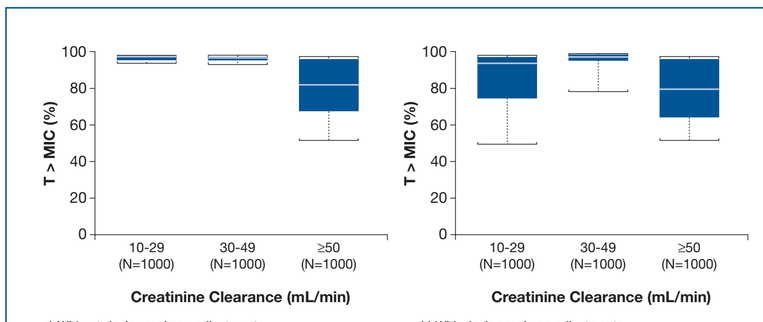
- The external model validation of the optimized full covariate model showed that the model (**Figure 1**) had good predictability for the observed concentrations in the test data set.
- PK parameter estimates from the final population PK model are presented in **Table 1** and the predictability diagnostic plots in **Figure 2**.

Figure 2. Visual predictive check of the final PK model.



- Of the covariates included in the model, only the renal function was identified as a clinically relevant factor using %T>MIC. Age (ie, ≥18 years old) was neither statistically nor clinically influential when creatinine clearance was included as a covariate.
- The distribution of %T>MIC without dosage adjustment (ie, using 500 mg, 2-h infusion, q8h) indicates high %T>MIC in the severe and moderate renal impairment groups (**Figure 3a**). With dosage adjustment based on creatinine clearance, unnecessarily high %T>MIC in these renally impaired populations would be avoided (**Figure 3b**).

Figure 3. Effect of dosage adjustment on %T>MIC.



a) Without dosing regimen adjustments
500 mg, q8h, 2-h infusion

b) With dosing regimen adjustments
CLcr ≥50 mL/min: 500 mg, q8h, 2-h infusion
30 ≤ CLcr <50 mL/min: 500 mg, q12h, 2-h infusion
10 ≤ CLcr <30 mL/min: 250 mg, q12h, 2-h infusion

- The influence on %T>MIC of sex, body weight, age, and health status on PK was negligible, with suggested dosing regimen adjustments based on degree of renal function (**Figure 4**).
- Exploratory analyses with race and concomitant medications as covariates suggested no change in PK of ceftobiprole due to these factors (**Figure 5**).

Figure 4. Influence of sex, health status, body weight, and age on %T>MIC.

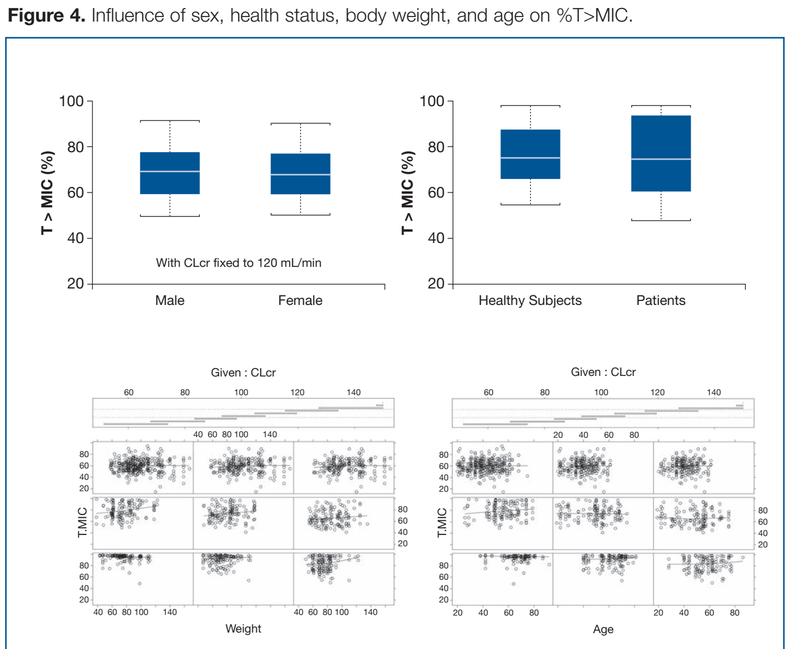
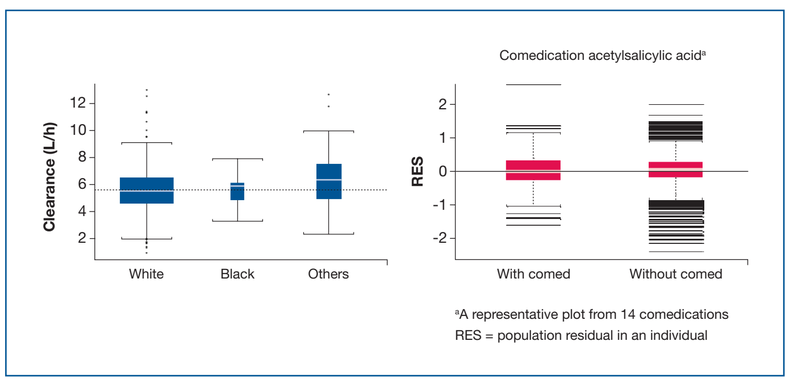


Figure 5. Race and comedication influence on PK.



[a]A representative plot from 14 comedications
RES = population residual in an individual

Conclusions

- **An open, three-compartment structural model described the individual PK profiles of ceftobiprole well.**
- **Ceftobiprole 500 mg every 8 h administered as a 2-h infusion is anticipated to provide reliable activity against most clinically important Gram-negative and Gram-positive pathogens, including MRSA.**
- **The population PK analysis indicates that ceftobiprole dosage adjustment should be based on creatinine clearance.**
- **No adjustments to ceftobiprole dosing are necessary for age, race, sex, body weight, or the assessed concomitant medications.**

References

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2. Lodise TP. Probability of target attainment for ceftobiprole as derived from a population pharmacokinetic analysis of 150 subjects. *Antimicrob Agents Chemother*. 2007 Mar 26; [Epub ahead of print]

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