Population Pharmacokinetic Analysis and Probability of Target Attainment Simulations of Pivmecillinam for the Treatment of Uncomplicated Urinary Tract Infection

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Objective

The objective of this analysis was to describe the pharmacokinetic of mecillinam after oral ingestion of pivmecillinam tablets and to investigate the effect of various dosing regimens on the probability of target attainment for mecillinam in the urine after pivmecillinam treatment.

Introduction

A population pharmacokinetic (PopPK) model was developed to characterize mecillinam (MEC) pharmacokinetics (PK) and urine exposure after intravenous (IV) administration of MEC or after oral (PO) administration of its prodrug pivmecillinam (PIV) in healthy subjects and patients with renal impairment (RI) or infections. MEC is a β-lactam antibiotic with a targeted spectrum of activity against Enterobacterales. The model was used to investigate various PIV treatment regimens and covariate scenarios on plasma exposure and urine excretion, and to perform probability of target attainment (PTA) simulations in support of dose justification for the treatment of uncomplicated urinary tract infection (uUTI).

Methods

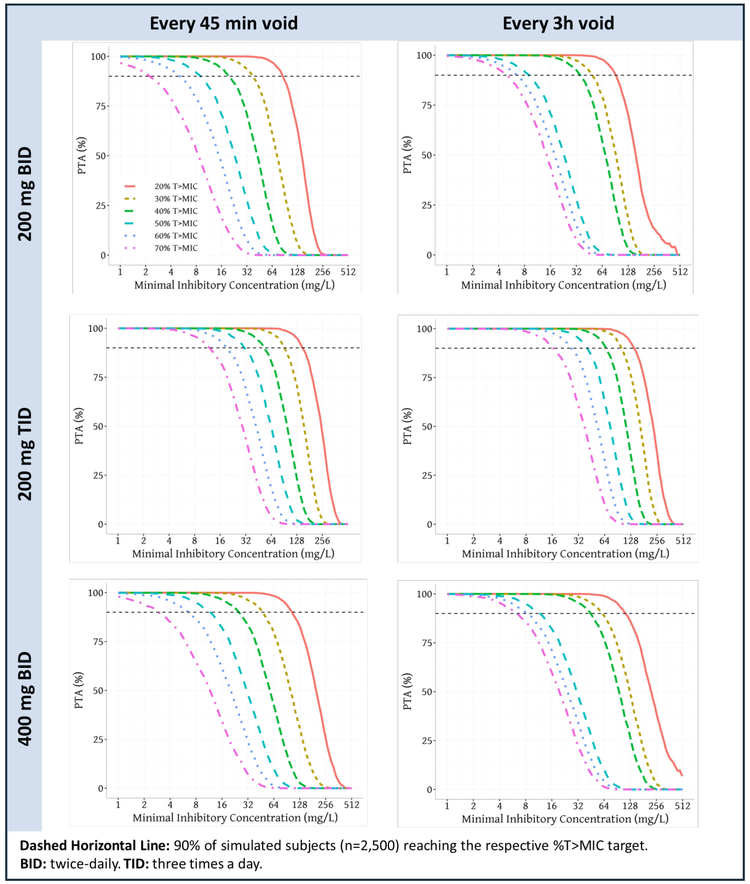
The analysis was based on MEC PK data obtained in plasma, serum, and urine in 15 clinical studies (**Table 1**). The dataset included a total of 3,964 plasma or serum concentrations and 989 urine samples obtained in 228 subjects. Those 228 subjects consisted of 172 healthy volunteers, 23 patients with infections (uUTI, Gram-negative infection, typhoid, or paratyphoid fever), and 33 patients with various degrees of RI. Subjects were treated with single or multiple doses of MEC (IV, 200-1,410 mg) or PIV (PO, 137-500 mg).

Table 1: Studies included in the PopPK analysis

Study Identifier	Type	N	Route and Dose (mg)	Population
LEO Pharma	Bioavailability tablets vs capsules	19	PO 400 PIV	HV
Bornemann et al., 1985, N2756A	Bioavailability, food effect	18	PO 400 PIV	HV
Bornemann et al., 1985, N2757A	Bioavailability and bioequivalence	18	PO 400 PIV	HV
Damsgaard et al., 1975	Absorption in patients	11	PO 600 PIV	Patients with urinary tract infections
Denneberg et al., 1975	Absorption in patients	20	PO 450 PIV	Patients with varying degrees of kidney function
Gustafson et al., 1980, 34843	Bioavailability	36	PO 400 PIV	HV
Holazo et al., 1981	PK and Bioavailability	12	PO 366/733 PIV and IV 500 MEC	HV
LEO Pharma, 1977	Absorption, food effect	9	PO 200 PIV	HV
Roholt, 1980	Bioavailability	10	PO 400 PIV	HV
Svarva & Wessel-Aas, 1980	Pharmacokinetics	12	IV 400 MEC	Patients with severe renal insufficiency
Patel et al., 1979	Pharmacokinetics	13	IV 15 mg/kg MEC	Healthy volunteers and patients with renal impairment
Duvauchelle et al., 1999	Bioavailability	18	PO 200 and 400 mg PIV	HV
Bukh, 1982	Pharmacokinetics	13	IV 200, 400, 800, and 1,200 MEC	HV
Holazo, 1981	Pharmacokinetics	12	IV 10 mg/kg MEC every 4 hours for 6 doses	HV
Kahlmeter, 1977	Pharmacokinetics	12	IV 300-1,000 mg MEC 4 times daily	Patients with gram-negative infection or typhoid, paratyphoid fever

Results

MEC PK profiles in plasma and urine were well characterized by a 2-compartment distribution model with first-order renal elimination and non-linear non-renal elimination. Oral absorption of PIV was best described using a single (Erlang) transit compartment. The PK model included parameter-covariate relationships for body weight on all clearance and volume parameters (with fixed allometric exponents of 0.75 and 1), a non-linear dose effect on bioavailability, formulation effects on absorption rate constant (k_a), food effects on both k_a and bioavailability, and effects of renal function on both clearance and Michaelis-Menten constant.



Dashed Horizontal Line: 90% of simulated subjects (n=2,500) reaching the respective %T>MIC target.
BID: twice-daily. **TID:** three times a day.

Figure 1: Predicted probability of target attainment in urine

PIV bioavailability was identified to decrease with increasing dose. As a result, MEC exposure was just 40% higher after administration of a PIV dose of 400 mg in comparison to a 200 mg dose. Administration of PIV under fed conditions resulted in an approximate 25% increase of the relative bioavailability and a 14% reduction of the oral absorption rate. MEC exposure was higher in patients with severe RI, 3.1 and 3.8-fold higher plasma $AUC_{0-12\,h}$ for a 200 mg dose at creatinine clearance values of 20 and 10 mL/min vs. 90 mL/min, and 3.8 and 3.4-fold higher trough concentration in urine, respectively.

In general, the impact of the covariates was most pronounced on the MEC plasma concentrations and was smaller when looking at the urine concentrations.

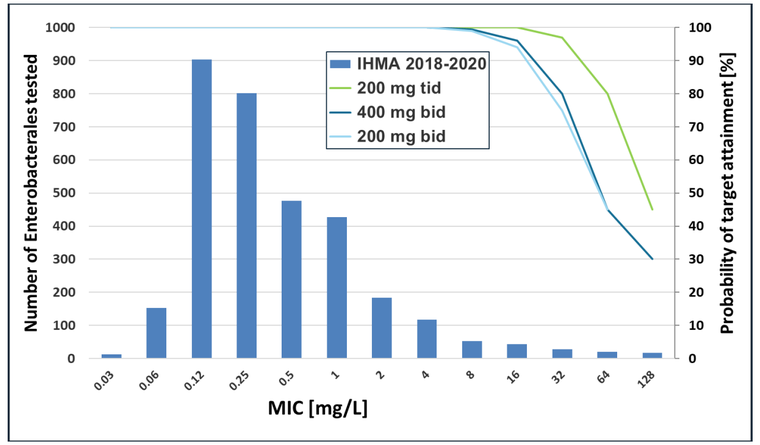


Figure 2: Pivmecillinam 200 mg TID achieved a PTA >95% for an MIC of 32 mg/L using a conservative target of 40% T>MIC

The final PopPK model was used to simulate 2,500 individual plasma and urine PK profiles after oral administration of 200 mg BID or TID, or 400 mg BID PIV and two urine voiding frequencies, every 3 hours, or every 45 minutes and using different %T>MIC targets (**Figure 1**). To ensure coverage of a wide range of Gram-negative pathogens the magnitude of %T>MIC has to be 40% or above. Using PopPK approaches, predicted PTA values demonstrate the adequacy of the 200 mg PIV TID regimen for coverage of pathogens with MIC≤32 mg/L in patients with uUTI (**Figure 2**).

Conclusion

- MEC PK was well characterized by a 2-compartment distribution model with first-order renal and non-linear non-renal elimination.
- The oral PIV absorption was best described using a single transit compartment. PTA simulations were supportive of a 200 mg TID dosing and a breakpoint of 32 mg/L for uncomplicated urinary tract infections

Disclosure

- Anne Santerre Henriksen is a consultant for UTILITY therapeutics.
- Hendrik Maxime Lagraauw, Marita Prohn, and Lars Lindbom are qPharmetra employees providing pharmacometric consultancy services to UTILITY therapeutics.

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