Poster # 597

Are We Dosing Correctly? Population Pharmacokinetic Modeling of Cefepime, Piperacillin-Tazobactam, and Meropenem in Individuals with Cystic Fibrosis

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INTRODUCTION

Patients with cystic fibrosis (CF) experience recurrent bacterial pulmonary exacerbations. The management of these infections becomes increasingly complex due to decreased antimicrobial susceptibility. The pharmacokinetics (PK) and pharmacodynamics (PD) of some of the most utilized antimicrobial agents for these infections, including cefepime, meropenem, and piperacillin-tazobactam, are inadequately characterized in this population, particularly for pediatric patients.

Objectives
- Define the PK of cefepime, meropenem, and piperacillin-tazobactam in subjects with CF using population PK analysis
- Simulate and evaluate the effect of various dosing regimens on the exposure profiles and target metrics of cefepime, meropenem, and piperacillin-tazobactam by using the population PK model
- Assess the potential effects of subject characteristics on PK parameters of cefepime, meropenem, and piperacillin-tazobactam in subjects with cystic fibrosis using population PK modeling and covariate analyses

METHODS

- One hundred fifty-five pediatric and adult participants receiving cefepime (n=82), meropenem (n=42), or piperacillin-tazobactam (n=31) were enrolled
- Opportunistic blood samples were obtained during hospitalization
- Population PK analysis was conducted using nonlinear mixed effects modeling in NONMEM, and clinical and demographic characteristics were evaluated as potential covariates
- Monte Carlo simulations evaluated the probability of PK/PD target attainment (PTA) for different dosing regimens with multiple targets, defined as percentage of a 24-h time period that the free drug concentration exceeds the MIC ($fT_{>MIC}$), based on prior studies of beta-lactam antibiotics

RESULTS

Breakpoints (mg/L, highest minimum inhibitory concentration (MIC) with ≥ 90% PK target attainment) for different infusion durations, based on Monte Carlo simulations

Table 1A: Cefepime breakpoints (mg/L) at which ≥90% of participants achieve targets				
	All participants	3 to 11 years	12 to 17 years	>17 years
Target 65% $fT_{>MIC}$				
0.5-h infusion	8	4	8	16
3-h infusion	16	16	16	16
Target 100% $fT_{>MIC}$				
0.5-h infusion	2	1	1	4
3-h infusion	4	2	4	8

Table 1B: Meropenem breakpoints (mg/L) at which ≥90% of participants achieve targets				
	All participants	$CL_{CR, LBW}$≥90	$CL_{CR, LBW}$<90	
Target 40% $fT_{>MIC}$	16	4	16	
Target 100% $fT_{>MIC}$	0.5	0.25	1	

Table 1C: Piperacillin breakpoints (mg/L) at which ≥90% of participants achieve targets				
	All participants			
Target 50% $fT_{>MIC}$				
4 g q8h 4-h infusion	16			
12 g/day continuous	16			
4 g q6h 4-h infusion	16			
16 g/day continuous	16			
Target 100% $fT_{>MIC}$				
4 g q8h 4-h infusion	0.125			
12 g/day continuous	16			
4 g q6h 4-h infusion	2			
16 g/day continuous	16			

RESULTS

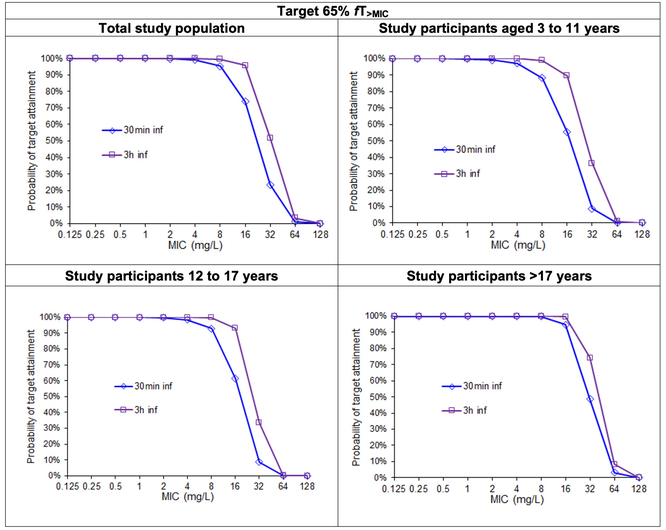
- Preliminary population PK modeling results show that lean body weight, creatinine clearance, daily dose, mode of administration (standard vs. extended infusion), and age affect PK parameters, with varying effects by drug
- As anticipated, extended or continuous infusions resulted in higher PTA

Cefepime
- The 3-h infusion regimen achieved higher PTAs than the 0.5-h regimen across all age groups
- Estimated breakpoints (in which ≥ 90% of patients are expected to achieve a PK/PD target) were 2-4 fold higher in pediatric participants receiving a 3-h infusion vs. 0.5-h infusion, based on age and target $fT_{>MIC}$

Meropenem
- Higher PTAs were achieved for the group with a $CL_{CR,LBW}$ of <90 mL/min, and lower PTAs were predicted for the group with a $CL_{CR,LBW}$ of ≥90 mL/min
- Increased creatinine clearance likely led to reduced PTA since meropenem is substantially excreted in the urine

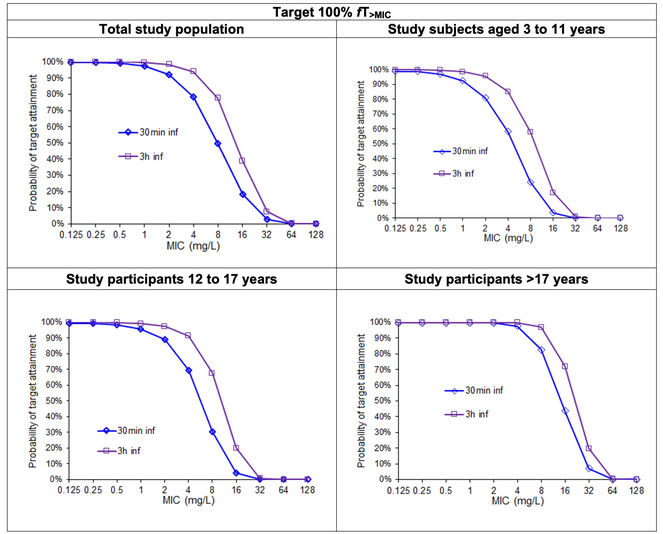
Piperacillin-tazobactam
- Total daily dose and interval were the principal drivers of PTA at the higher target of 100% $fT_{>MIC}$

Comparison of PTA between the two durations of infusion for 50 mg/kg (3 to 11 years) or 2 g (12 years and above) cefepime q8h at the target of 65% $fT_{>MIC}$



RESULTS

Comparison of PTA between the two durations of infusion for 50 mg/kg (3 to 11 years) or 2 g (12 years and above) cefepime q8h at the target of 100% $fT_{>MIC}$



CONCLUSIONS

To our knowledge, this is the largest population PK study to date of cefepime, meropenem, and piperacillin-tazobactam in individuals with CF. Clinicians should incorporate local antibiograms with these population PK models to determine optimal dosing in patients with CF, since standard dosing regimens may fail to achieve specific PK/PD targets. The use of extended infusions in patients with CF who are 3 to 17 years old, where clinically practical, may be beneficial for PK/PD target achievement, particularly for resistant pathogens with high MICs. Since many clinical and demographic covariates affect PK parameters, this population may also benefit from beta-lactam therapeutic drug monitoring for individualized therapy.

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