Cefepime Pharmacokinetics in in Adolescent and Young Adult Cystic Fibrosis Patients

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Abstract

•Introduction: The treatment of acute pulmonary exacerbations (APEs) in Cystic Fibrosis (CF) requires dual therapy, typically with regimens containing an anti-pseudomonal β-lactam. Optimal β-lactam dosing regimens in pediatric CF patients are not well described. We aimed to evaluate the pharmacokinetics (PK) of cefepime (CEF) in pediatric CF patients admitted for the treatment of an APE.

•Methods: This was a PK study of hospitalized pediatric CF patients that received CEF either as a 0.5 hr intermittent infusion (II) or 18 hour continuous infusion (CI) for treatment of an APE from November 2014-March 2015. Patients contributed 2-3 blood samples for CEF concentration determination. CEF concentrations were determined by liquid chromatography/tandem mass spectroscopy. A non-compartmental PK analysis was conducted to determine the elimination rate constant (k_e), half-life ($t_{1/2}$), and volume of distribution (Vd). The % of the dosing interval with free drug concentrations above the MIC (*f*T>MIC) was calculated using an MIC of 8 and 16 mcg/mL. Bactericidal exposure was defined as ≥ 50% *f*T>MIC. The probability of target attainment (PTA) > 90% for each MIC was defined as optimal.

•Results: 7 patients contributed 16 CEF concentrations. The median age was 4 yrs (range 2-9 yrs). Mean weight was 20.5 ± 0.94 kg. 4 of 7 patients received CEF as II of 50 mg/kg/dose IV q6h and 3 of 7 patients received 200 mg/kg/day 18-hr CI. The mean ± SD k_e was 0.46 ± 0.2 hr^{-1}. The mean ± SD $t_{1/2}$ was 1.8 ± 0.9 hrs as compared to a reported $t_{1/2}$ of 2-4 hrs in non-CF pediatric patients. Of the 4 patients receiving II, none had an appropriate PTA at the MICs of 8 and 16 mcg/mL. Of the 3 patients receiving 18-hr CIs, all achieved target PTA at the MICs of 8 and 16. Using the mean PK parameters from this cohort, an 18-hr CI of 175 mg/kg/day is needed is needed to achieve a serum level 8x the intermediate breakpoint of 16 mcg/mL and 350 mg/kg/day for the resistant breakpoint of 32 mcg/mL. If 24-hr CIs were used, the total daily doses needed would increase to 240 and 470 mg/kg/day, respectively.

•Conclusion: These data suggest the CEF PK in pediatric CF patients is different than non-CF pediatric patients. Standard intermittent dosing regimens do not result in serum concentrations that achieve a 90% PTA for a bactericidal exposure. 18 and 24-hr CI regimens of do provide for an appropriate PTA with doses ranging from 175-470 mg/kg/day depending on the MIC.

Introduction

- The treatment of acute pulmonary exacerbations (APEs) in Cystic Fibrosis (CF) requires dual therapy
- Regimens commonly contain an anti-pseudomonal β-lactam with an aminoglycoside
- Optimal β-lactam dosing regimens in pediatric CF patients are not well described

Objective

- We aimed to evaluate the pharmacokinetics (PK) of cefepime (CEF) in adolescent and young adult CF patients admitted for the treatment of an APE

Methods

- Pediatric CF patients that received CEF either as a 0.5 hr intermittent infusion (II) or 18 hour continuous infusion (CI) from November 2014-March 2015.
- Patients contributed 2-3 blood samples for CEF concentration determination.
- Concentrations for CEF in serum were determined by LC-MS/MS
- The method was proven to be accurate and precise at linearity range of 5 - 500 µg/mL with a correlation coefficient (r) of >or=0.990.
- The method was rugged with 5 µg/mL as lower limit of quantitation
- The inter-day assay variability was less than 15% across all reference samples between 5 and 500 µg/mL
- In the event samples were outside the upper limit of determination on the standard curve, a 1:2 or 1:10 dilution was made until the sample was within the standard curve
- If samples were below the lower limit of quantitation on the standard curve, a value of "less than 5 µg/mL" was reported by the reference laboratory

Methods

- Elimination rate constant (k_e), half-life ($t_{1/2}$), and volume of distribution (Vd) were determined by non-compartmental pharmacokinetic analysis
- The % of the dosing interval with free drug concentrations above the MIC (*f*T>MIC) was calculated using an MIC of 8 and 16 mcg/mL
- Bactericidal exposure was defined as ≥ 50% *f*T>MIC
- The probability of target attainment (PTA) > 90% for each MIC was defined as optimal

Results

- 7 patients contributed 16 CEF concentrations
- Median age was 15 years (range 15-22 years)
- 3 patients received II, 50 mg/kg/dose IV q6h
  - All had an appropriate PTA for a bactericidal exposure at an MIC of 8 or 16 mcg/mL
- 4 patients received 18-hr CI
  - All had an appropriate PTA for a bactericidal exposure at an MIC of 8 or 16 mcg/mL

Table 1. Demographic Information

Pt	Age	Sex	Weight (kg)	Dose (mg)	Dose (mg/kg)	Interval (hr)
1	15	M	47.9	2000	41.75365	6
2	15	F	41.7	8000	191.8465	18
3	15	M	50.8	8000	157.4803	18
4	15	M	50.8	12000	236.2205	18
5	16	M	59	8000	135.5932	18
6	20	M	69.7	2000	28.6944	6
7	22	F	51.8	2000	38.61004	6

Results

Table 2. Individual PK Parameters

Pt	Co (mcg/mL)	Ke (hr^{-1})	Half life (hrs)	Vd (L)	Vd (L/kg)	CL (L/hr/kg)
1	197.6	0.41	1.69	10.1	4.1	0.08
2	212	0.68	1	30.7	20.9	0.5
3	56	0.61	1.1	13	7.9	0.16
4	493	0.78	0.9	1.72	1.3	0.03
5	36.9	0.5	1.3	23	11.9	0.2
6	654	0.68	1	3	2.1	0.03
7	960	0.75	0.9	2	1.5	0.03
Mean	372.8	0.63	1.1	11.9	7.1	0.14
St Dev	343.5	0.13	0.28	11.3	7.2	0.17
Median	212	0.68	1	10.1	4.1	0.08
Min	36.9	0.41	0.9	1.7	1.3	0.03
Max	960	0.78	1.69	30.7	20.8	0.5

Conclusion

- These data suggest the CEF PK in adolescent and young adult CF patients is different than non-CF patients
- Standard intermittent dosing regimens do not result in serum concentrations that achieve a 90% PTA for a bactericidal exposure
- An every 6 hour dosing regimen does provide for a 90% PTA for a bactericidal exposure
- 18 and 24-hr CI regimens also provided for an appropriate PTA

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