Pharmacokinetics of ceftobiprole in paediatric patients

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Introduction and Purpose

Ceftobiprole medocaril (prodrug of the active moiety ceftobiprole) is a broad-spectrum cephalosporin with bactericidal activity against a broad range of Gram-positive and Gram-negative pathogens, including *Pseudomonas aeruginosa* and both methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) strains of *Staphylococcus aureus.*

Indications

Currently approved in 13 European countries and Canada for the treatment in adults of:

- Community-acquired pneumonia (CAP)
- Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)

Standard adult dosing regimen

- 500 mg as a 2-hour IV infusion q8h
- Dose-adjustment for renal impairment

Purpose

Ceftobiprole is not approved for patients aged <18 years. This Phase 1 open-label study evaluated the pharmacokinetics (primary objective), safety, and tolerability of a single dose of ceftobiprole in paediatric patients requiring systemic antibiotics.

Methods

Animal models of infection indicated that %T>MIC of the free-fraction was the primary pharmacodynamic driver of efficacy and that for Gram-positive pathogens including MRSA, serum trough concentrations needed to exceed the pathogen MIC for > 30% of the dosing interval.

To define an appropriate dosing strategy, a target pathogen MIC of 4 µg/mL was chosen, based on recent surveillance studies which showed ceftobiprole MIC_{90} for MRSA to be 2 µg/mL.

Ceftobiprole was administered as a 2-hour infusion in patients aged 3 months–<18 years. A sequential dosing approach was taken in which the safety of ceftobiprole was confirmed in older adolescents and children before proceeding with administration in younger children and infants.

Dose levels to characterise ceftobiprole PK in children were chosen with the assumption that that drug clearance steadily increases as age decreases:

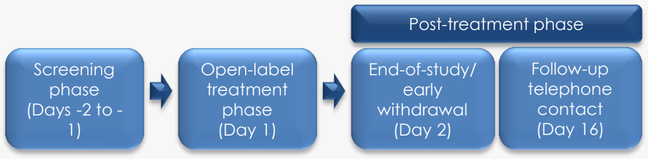
- ≥ 12 and < 18 years of age: 7 mg/kg (assumes drug clearance is similar between adolescents and adults; equivalent to an adult dose of 500 mg)
- ≥ 6 and <12 years of age: 10 mg/kg (equivalent to an adult dose of 750 mg)
- < 6 and ≥ 2 years of age: 15 mg/kg (equivalent to an adult dose of 1050 mg)
- < 2 year and ≥ 3 months of age: 15 mg/kg (equivalent to an adult dose of 1050 mg)

No subject was to receive a dose greater than 500 mg.

Blood and urine samples were collected over 24 hours following the start of infusion, and analysed by LC-MS/MS. Safety assessments were based on the incidence, type, severity, and relationship to study drug of reported treatment-emergent adverse events and pretreatment to end-of-study changes in clinical laboratory tests, vital sign measurements, and physical examinations.

Study design

Multi-center, open-label, single-dose.



Results

Table 1: Demographics of the pharmacokinetic analysis population*

	3 m – < 2 y N=13	2 – < 6 y N=13	6 – < 12 y N=15	12 – < 18 y N=14
Mean age [range] (years)	1.07 [0.36-1.83]	4.27 [2.15-5.86]	9.27 [6.62-11.7]	15.3 [12.4-17.9]
Mean weight ± SD (kg)	10.3 ± 2.47)	18.1 ± 3.77)	33.8 ± 9.40)	60.3 ± 12.4)
Mean height ± SD (cm)	74.5 ± 8.68)	104 ± 12.1)	137 ± 10.3)	166 ± 13.3)
Mean BMI ± SD (kg/m²)	18.4 ± 1.76)	16.8 ± 2.64)	17.8 ± 3.46)	21.6 ± 2.99)
Sex (n [%]) Male	8 [62]	7 [54]	8 [53]	9 [64]
Female	3 [38]	6 [46]	7 [47]	5 [36]

*Data for six patients were excluded from the PK-parameter estimation analyses due to insufficient sample volumes, or incorrect sampling times

Pharmacokinetics

- Of the 62 patients who completed the study, 61 were included in the descriptive statistics and 55 were included in the PK-parameter estimations (Table 1)
- Ceftobiprole PK in paediatric patients were generally within the range of those for adults (Table 2) and were very similar between the age groups (Figure 1)
- Paediatric mean C_{max} and AUC_{∞} values relative to adults:
  - C_{max} and AUC_{∞}values for subjects aged 3 months to <12 years approximated those of adults (Table 2)
  - In subjects aged 12–<18 years, AUC_{∞} values were slightly lower than for adults (~20%) and C_{max} values were ~40% lower (Table 2)
- Mean Vd_{ss} and CL decreased with increasing age (body-weight adjusted)
- Elimination $t_{½}$ (not adjusted for body weight) and CL_{CR} were similar across age groups
- Body-weight normalized ceftobiprole clearance showed a decreasing trend with increasing age (Figure 2)
- Ceftobiprole concentrations were on average above the MIC (4 µg/mL) for 66.5–75.3% of an 8-hour time period (%T>MIC)

Figure 1: Mean ceftobiprole plasma concentration-time linear-linear profiles (PK population)

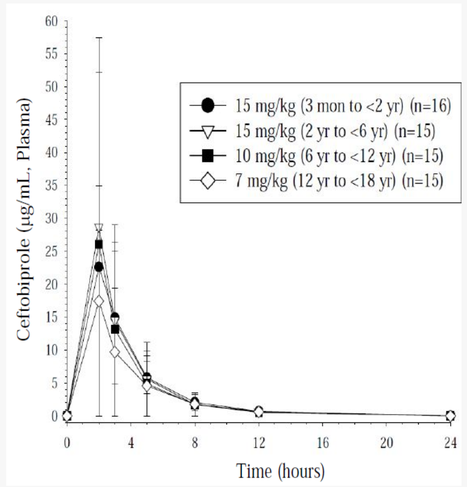
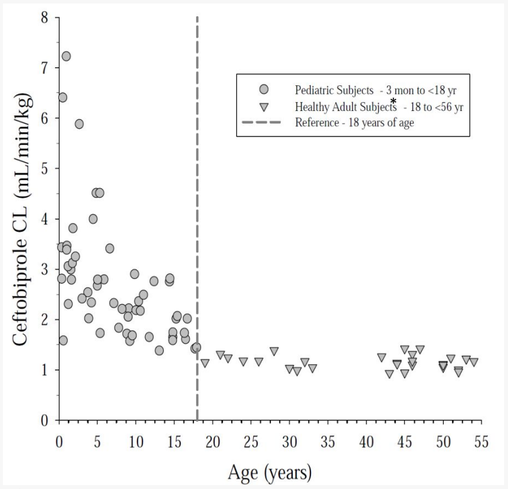


Figure 2: Body weight-normalized ceftobiprole clearance in paediatric and adult* subjects (PK population)



*Murthy et al. ECCMID 2007:P779

Safety

- Ceftobiprole was well tolerated in paediatric patients
- No subjects discontinued due to treatment-emergent AEs
- Eight subjects reported 14 serious adverse events (SAEs) during the study (Table 3)
- None of the SAEs occurred in > 1 subject and none were considered by the investigator to be treatment-related

Table 2: Pharmacokinetic parameters of ceftobiprole per paediatric age group (PK population)

	3 m – < 2 y 15 mg/kg N=13	2 – < 6 y 15 mg/kg N=13	6 – < 12 y 10 mg/kg N=15	12 – < 18 y 7 mg/kg N=14	≥ 18 y[1] 500 mg N=28
C_{max} (µg/mL)	24.4 ± 9.1	28.7 ± 7.0	25.2 ± 4.9	17.4 ± 3.2	29.2 ± 5.5
AUC_{∞} (µg·h/mL)	80.7 ± 30.0	87.7 ± 28.2	79.5 ± 16.2	63.5 ± 14.3	104 ± 13.9
Elimination $t_{½}$ (h)	2.1 ± 0.8	2.1 ± 0.4	2.2 ± 0.5	2.4 ± 0.5	3.1 ± 0.3
Vd_{ss} (L) [Vd_{ss}/BW] (L/kg)	6.7 ± 3.6 [0.63 ± 0.29]	10.0 ± 3.8 [0.56 ± 0.21]	13.8 ± 5.2 [0.41 ± 0.11]	23.0 ± 3.67 [0.39 ± 0.07]	21.7 ± 3.4
CL (L/h) [CL/BW] (mL/min/kg)	2.3 ± 1.2 [3.6 ± 1.6]	3.4 ± 1.3 [3.2 ± 1.2]	4.4 ± 1.3 [2.2 ± 0.5]	6.7 ± 1.1 [1.9 ± 0.5]	4.8 ± 0.7
CL_R (L/h) [CL_R/BW] (mL/min/kg)	1.5 ± 1.0[a] [2.3 ± 1.5][a]	2.4 ± 1.7 [2.1 ± 1.4]	4.6 ± 3.5 [2.2 ± 1.3]	5.6 ± 1.8 [1.6 ± 0.7]	4.1 ± 0.7
%T>MIC (4 mg/L)[b]	75.3 (32.7 – 93.2)	73.5 (47.7 – 97.7)	66.5 (50.7 – 91.3)	68.6 (46.3 – 84.9)	78.2 (62.3 – 90.1)

Data are mean ± SD, unless otherwise stated.
Data for six patients were excluded from these analyses due to insufficient sample volume, or incorrect sampling times
BW, body weight; C_{max}, max. plasma concentration; AUC, area under the plasma concentration-time curve; $t_{1/2}$, half-life; Vd_{ss}, apparent volume of distribution; CL, total clearance; CL_R, renal clearance; T>MIC, time plasma-concentrations are above the MIC level of 4 µg/mL; %T>MIC, percentage of 8-hour dosing interval represented by T>MIC.
[a]n=12; [b]median (range).
[1]Murthy et al. ECCMID 2007:P779

Table 3: Serious treatment-emergent adverse events per paediatric age group (safety population)

	Serious treatment-emergent* adverse events n (%)				
Dictionary-derived term	3 m – < 2 y 15 mg/kg (N=18)	2 – < 6 y 15 mg/kg (N=15)	6 – < 12 y 10 mg/kg (N=15)	12 – < 18 y 7 mg/kg (N=16)	Total (N=64)
Total no. subjects with SAEs	0	3 (20.0)	1 (6.7)	4 (25.0)	8 (12.5)
Aspiration	0	1 (6.7)	0	0	1 (1.6)
Cough	0	0	1 (6.7)	0	1 (1.6)
Dyspnoea	0	0	0	1 (6.3)	1 (1.6)
Wheezing	0	1 (6.7)	0	0	1 (1.6)
Empyema	0	0	0	1 (6.3)	1 (1.6)
Enterococcal bacteraemia	0	0	0	1 (6.3)	1 (1.6)
Dehydration	0	1 (6.7)	0	0	1 (1.6)
Hypovolaemia	0	0	0	1 (6.3)	1 (1.6)
Abdominal pain	0	1 (6.7)	0	0	1 (1.6)
Vomiting	0	1 (6.7)	0	0	1 (1.6)
Pyrexia	0	1 (6.7)	0	0	1 (1.6)
Post-procedural haemorrhage	0	0	0	1 (6.3)	1 (1.6)
Unresponsive to stimuli	0	1 (6.7)	0	0	1 (1.6)
Explorative laparotomy	0	1 (6.7)	0	0	1 (1.6)

No subject discontinued due to treatment-emergent adverse events.
*None of the SAEs were considered to be treatment-related by the Investigator

Conclusions

A single dose of ceftobiprole in the dose range of 7–15 mg/kg was well tolerated in pediatric subjects ≥ 3 months to < 18 years of age.

Single-dose PK were within the range of those for healthy adults; for individuals aged 12–<18 years, ceftobiprole exposure was lower than in adults. However, for all age groups the PK/PD driver was in a similar range to that of adults for the selected doses. These data should be considered when designing future paediatric studies.

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