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Paper Poster Session
PK/PD of agents against Gram-negatives

Pharmacokinetics of ceftobiprole in paediatric patients

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Background: Ceftobiprole medocaril (the prodrug of the active moiety ceftobiprole) is a broad-spectrum cephalosporin for hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults; the standard dose is 500 mg administered as a 2-hour intravenous infusion every 8 hours. Ceftobiprole is not approved for patients aged <18 years. This open-label study evaluated the pharmacokinetics (primary objective), and safety and tolerability of a single dose of ceftobiprole in paediatric patients requiring systemic antibiotics.

Material/methods: Ceftobiprole was administered as a 2-hour infusion in patients aged 3 months–<18 years. Doses were adjusted to achieve exposures equivalent to those in adults following standard dosing: 15 mg/kg for patients aged 3 months–<2 years and 2–<6 years; 10 mg/kg for those aged 6–<12 years; and 7 mg/kg for individuals aged 12–<18 years. Blood and urine samples were collected over 24 hours following the start of infusion, and analysed by LC-MS/MS.

Results: Sixty-four patients were enrolled (mean age, 7.3 years; boys, 56.3%); 55 were included in the pharmacokinetics analysis. Ceftobiprole pharmacokinetics in paediatric patients were broadly within the range of those for adults[1] (Table). Mean C_{max} and AUC_{∞} were up to ~20% lower in patients aged <12 years (24.4–28.7 µg/mL and 79.5–87.7 µg·h/mL, respectively) than in adults (29.2 µg/mL and 104 µg·h/mL, respectively[1]). In patients aged 12–<18 years, mean C_{max} and AUC_{∞} (17.4 µg/mL and 63.5 µg·h/mL, respectively) were ~40% lower than in adults.[1] When adjusted for body weight, mean Vd_{ss} and CL decreased with increasing age, while elimination $t_{½}$ (not adjusted for body weight) and CL_R were similar across age groups. Ceftobiprole concentrations were above the MIC (4 µg/mL) for 66.5–75.3% of an 8-hour time period (%T>MIC). Ceftobiprole was generally well tolerated in paediatric patients.

Conclusions: Ceftobiprole pharmacokinetics in paediatric patients were broadly within the range of those for adults; however, for individuals aged 12–<18 years, ceftobiprole exposure was substantially lower than in adults. These data should be considered when designing studies.

	3 months–<2 years **15 mg/kg** **n=13**	**2–<6 years** **15 mg/kg** **n=13**	**6–<12 years** **10 mg/kg** **n=15**	**12–<18 years** **7 mg/kg** **n=14**	**≥18 years[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,c]	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. [a]n=12; [b]Median (range); [c]8-h dosing interval.

[1]Murthy *et al.* ECCMID 2007:P779.