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Pharmacokinetics and Safety of Ceftobiprole in Pediatric Patients

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Background: Ceftobiprole, the active moiety of the prodrug ceftobiprole medocaril, is an advanced-generation, broad-spectrum, intravenous cephalosporin, which is currently approved for the treatment of adults with hospital-acquired or community-acquired pneumonia.

Methods: Noncompartmental pharmacokinetics and safety were analyzed from 2 recently completed pediatric studies, a single-dose, phase 1 study in neonates and infants up to 3 months of age (7.5 mg/kg) and a phase 3 study in patients 3 months to 17 years of age with pneumonia (10–20 mg/kg with a maximum of 500 mg per dose every 8 hours for up to 14 days).

Results: Total ceftobiprole plasma concentrations peaked at the end of infusion. Half life (median ranging from 1.9 to 2.9 hours) and overall exposure (median AUC ranging from 66.6 to 173 μg•h/mL) were similar to those in adults (mean ± SD, 3.3 ± 0.3 hours and 102 ± 11.9 μg•h/mL, respectively). Calculated free-ceftobiprole concentrations in the single-dose study remained above a minimum inhibitory concentration (MIC) of 4 mg/L (fT > MIC of 4 mg/L) for a mean of 5.29 hours after dosing. In the pneumonia study, mean fT > MIC of 4 mg/L was ≥5.28 hours in all dose groups. Ceftobiprole was well tolerated in both studies.

Conclusions: Pharmacokinetic parameters of ceftobiprole characterized in the pediatric population were within the range of those observed in adults. In the pneumonia study, the lowest percentage of the dosing interval with fT > MIC of 4 mg/L was 50.8%, which suggests that pharmacokinetic-pharmacodynamic target attainment can be sufficient in pediatric patients. Ceftobiprole was well tolerated.

Key Words: ceftobiprole, cephalosporin, pharmacokinetics, noncompartmental analysis, pediatric patients

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Ceftobiprole is the active moiety of the prodrug ceftobiprole medocaril and is an advanced-generation intravenous (IV) cephalosporin with broad activity against Gram-positive and Gram-negative organisms including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *S. aureus*, penicillin-resistant *Streptococcus pneumoniae*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*.[1–3] It is approved for the treatment of hospital-acquired pneumonia, excluding ventilator-associated pneumonia, and community-acquired pneumonia in adults in many European and non-European countries.[4] Ceftobiprole is currently under investigation to support a New Drug Application in adults in the United States for acute bacterial skin and skin structure infections and *S. aureus* bacteremia, including infective endocarditis.[5,6] The spectrum of activity and well-established safety profile of ceftobiprole make it an attractive candidate for the treatment of infections in the pediatric population.[3,7]

The pharmacokinetics (PK) of ceftobiprole have been established in adults in both healthy volunteers and infected patients.[8–11] In adults, ceftobiprole exhibits linear PK across a broad range of IV doses and exhibits limited accumulation with repeated dosing because of its short half life ($T_{1/2}$) of approximately 3 hours.[4,8,9] Ceftobiprole undergoes minimal hepatic metabolism and is rapidly eliminated, primarily unchanged, by glomerular filtration, with 80–90% of the dose recovered in urine. The primary metabolite is the β-lactam ring-opened hydrolysis product (open-ring metabolite), which accounts for 5% of the dose recovered in urine[12]; systemic exposure of the open-ring metabolite accounts for 4% of ceftobiprole exposure following single-dose administration. Although several patient characteristics have been identified as predictive of the interindividual variability in ceftobiprole PK in adults (eg, infected vs healthy, sex, body weight), only renal function is considered clinically relevant such that dosage adjustment is recommended in patients with moderate or severe renal impairment.[4,10] Similar to other β-lactam antibiotics, the duration of time after dose that free-drug concentrations remain above the minimum inhibitory concentration (MIC) of an infecting organism (fT > MIC) is the main pharmacokinetic-pharmacodynamic (PK-PD) index.[13]

A thorough evaluation of the PK of ceftobiprole in pediatric patients is critical to substantiating appropriate dosing in this population.[14,15] To date, minimal data have been published regarding the PK of ceftobiprole in pediatric patients.[16] Thus, a primary aim of these analyses was to describe the PK of ceftobiprole using data collected from 2 recently completed pediatric studies, BPR-PIP-001 and BPR-PIP-002. In addition, the safety and tolerability of ceftobiprole in patients enrolled in Study BPR-PIP-001 will be described along with a brief overview of the safety of ceftobiprole in Study BPR-PIP-002, which has been described in full previously.[17]

MATERIALS AND METHODS

Study BPR-PIP-001

Study BPR-PIP-001 was a multicenter, open-label, single-dose, phase 1 study conducted to evaluate the PK and safety of ceftobiprole in neonates and infants up to 3 months of age undergoing treatment with systemic antibiotics (ClinicalTrials.gov identifier: NCT02527681; EudraCT number: 2013-004614-18).[18] A total of 45 subjects, stratified for gestational and age (GA) and postnatal age, were to be enrolled in 3 sequential cohorts: (1) full-term infants (GA ≥37 weeks), (2) infants with GA 33–36 weeks, and (3) infants with GA of 28–32 weeks. Because of slow enrollment, the study was completed after enrollment of the full-term cohort and with no preterm subjects enrolled. All subjects received a single dose of IV ceftobiprole 7.5 mg/kg administered over 4 hours, which was selected as a conservative dose with a high margin of safety given that (1) the primary objective of this study was to evaluate the PK of ceftobiprole in this age group and (2) subjects were on standard-of-care antibiotics during the study; therefore, there was no expectation that ceftobiprole exposure would be effective clinically.

Treatment-emergent adverse events (TEAEs) were defined as any adverse events (AEs) occurring between administration of the study medication and the follow-up visit on day 7 ± 3 days. Blood and urine samples were analyzed for safety laboratory parameters at screening and the follow-up visit on day 7 ± 3 days. Vital signs were measured within 15 minutes predose and at 1, 2.25, and 6 hours after the start of infusion. Physical examination was performed at screening, day 1, and day 7 ± 3 days.

Blood samples for PK analysis were obtained predose and at 2, 4, 6, 8, and 12 hours after the start of dosing. Urine samples were collected before, during, and after dosing. Plasma and urine were analyzed for total concentrations of ceftobiprole, ceftobiprole medocaril, and the open-ring metabolite using a validated gradient reversed-phase liquid chromatography-tandem mass spectrometry.[8,9]

Study BPR-PIP-002

Study BPR-PIP-002 was a multicenter, randomized, investigator-blinded, active-controlled, phase 3 study to evaluate the safety, tolerability, PK, and efficacy of ceftobiprole versus IV standard-of-care cephalosporin treatment with or without vancomycin in pediatric patients from 3 months to 17 years of age with hospital-acquired pneumonia or community-acquired pneumonia requiring hospitalization (ClinicalTrials.gov identifier: NCT03439124; EudraCT number: 2013-004615-45).[17,19] A total of 138 patients, randomized 2:1 to ceftobiprole (n = 94) or standard-of-care comparator (n = 44), were enrolled, with 70 patients under 6 years and 68 patients 6 years or older. Patients randomized to ceftobiprole received IV ceftobiprole every 8 hours for a minimum of 3 days. Infants 3 months to less than 2 years of age received 20 mg/kg administered over 4 hours. Children 2–5 years of age received 20 mg/kg administered over 2 hours, and children 6–11 years of age received 15 mg/kg administered over 2 hours. Adolescents 12–17 years of age received 10 mg/kg administered over 2 hours. The maximum allowable dose was 500 mg regardless of patient weight. After 3 days, patients could have been switched to an oral antibiotic to complete a minimum of 7 days and a maximum of 14 days of antibiotic therapy. The doses for this study were selected based upon (1) PK and safety data obtained from a single-dose study conducted in pediatric subjects 3 months to less than 2 years of age who received IV ceftobiprole 15 mg/kg,[16] (2) results of toxicity studies in juvenile animals (data on file, Basilea), and (3) model-based simulations conducted to identify a dose likely to result in ceftobiprole exposure that has been associated with efficacy and safety in adults (data on file, Basilea).

TEAEs were monitored through the last follow-up visit, 28–35 days after end of treatment (EOT). Vital signs were assessed 3 times daily during active study drug treatment, and at EOT visit within 24 hours of last study drug administration and the test-of-cure visit 7–14 days after EOT.

Blood samples for PK analysis were obtained on day 3 as follows: patients 2 years of age and older had samples collected predose and 2 (end of infusion), 4, 6, and 8 hours after start of infusion. Patients less than 2 years of age had samples collected predose and 4 (end of infusion), 6, and 8 hours after start of infusion. Plasma was analyzed for total concentrations of ceftobiprole, ceftobiprole medocaril, and the open-ring metabolite using the liquid chromatography-tandem mass spectrometry assay described above.[8,9]

Ethics

Studies BPR-PIP-001 and BPR-PIP-002 were conducted in compliance with relevant local laws/regulations, ICH Good Clinical Practice guidelines, and the amended Declaration of Helsinki. An Independent Ethics Committee/Institutional Review Board at each site approved the study protocol and a Data Safety Monitoring Board monitored the safety data to ensure patient safety. Each child's parent or legal guardian provided written informed consent. If appropriate, the child's assent was also sought before participation in the trial.

Noncompartmental PK Analysis

All dataset creation, graphical presentations of data, and calculation of PK parameters (detailed below) were conducted using R, version 3.6.1.[20] For the purposes of plotting the data and calculating PK parameters, plasma and urine concentration values that were below the lower limit of quantification were set to missing.

PK parameters were calculated using the actual times of sample collection. Maximum observed plasma concentration (C_{max}) and time of maximum observed plasma concentration (T_{max}) were derived directly from the serum concentration-time data. Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration ($AUC_{0\text{-}last}$) was calculated by the trapezoidal rule (linear up, log down). Area under the plasma concentration-time curve from time zero to the end of the dosing interval ($AUC_{0\text{-}tau}$) was calculated by the trapezoidal rule (Study BPR-PIP-002 only). The fT > MIC of 4 mg/L was calculated using a reported plasma protein-binding estimate of 16%.[12] The percentage of the dosing interval for which free-drug concentrations remained above an MIC of 4 mg/L (%fT > MIC of 4 mg/L) was also calculated with an assumed plasma protein-binding estimate of 16% (Study BPR-PIP-002 only). An MIC of 4 mg/L was selected based on the most conservative European Committee on Antimicrobial Susceptibility Testing ceftobiprole nonspecies-specific PK-PD breakpoint (Enterobacterales, 0.25 mg/L; *S. aureus*, 2 mg/L; *S. pneumonia*, 0.5 mg/L; nonspecies-specific PK-PD breakpoint, 4 mg/L).[21]

The following PK parameters were also calculated where possible: the apparent terminal elimination rate constant (λ_z) was calculated from a semilog plot of the plasma concentration versus time curve by linear least squares regression analysis using the maximum number of points in the terminal log-linear phase using an automated method. The apparent terminal elimination $T_{1/2}$ was calculated as the natural log of 2 divided by λ_z. Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0\text{-inf}}$) was calculated as $AUC_{0\text{-last}}$ plus the last observed concentration (C_{last}) divided by λ_z. $AUC_{0\text{-inf}}$ was set to missing if λ_z could not be calculated (Study BPR-PIP-001 only). Systemic clearance (CL) was estimated as Dose/$AUC_{0\text{-inf}}$ (Study BPR-PIP-001 only). Volume of distribution (V_d) was estimated as Dose/($AUC_{0\text{-inf}} \cdot \lambda_z$) (Study BPR-PIP-001 only). Volume of distribution at steady state (V_{SS}) was estimated by mean residence time multiplied by CL. The percentage of the administered dose excreted over the urine collection interval (Ae) was calculated as the total amount excreted over the 12-hour period divided by dose and expressed as a percent (Study BPR-PIP-001 only). Clearance at steady state (CL_{SS}) was calculated as dose divided by $AUC_{0\text{-tau}}$ (Study BPR-PIP-002 only). The accumulation ratio ($R_{accumulation}$) was calculated as $1/(1 - e^{-\lambda z \cdot tau})$. For the open-ring metabolite, the dose-dependent parameters (CL, CL_{SS}, V_d, and V_{SS}) were conditioned on the unknown fraction of the dose that is converted to the metabolite.

Summary statistics (number, mean, percent coefficient of variation, median, minimum, and maximum) were tabulated by analyte for the PK parameters.

Data Availability

After publication, the data will be made available to others on reasonable request to Basilea Pharmaceutica International Ltd.

RESULTS

Noncompartmental PK Analysis

Study BPR-PIP-001

Plasma concentration-time data were available for the 15 subjects enrolled in Study BPR-PIP-001. The observed concentration-time profiles for all 3 analytes are shown in Figure 1. As expected, concentrations of ceftobiprole medocaril were low overall and fell below the limit of quantification by 4 hours in all but 1 subject. Parent drug (ceftobiprole) concentrations peaked at 4 hours (ie, at the end of the infusion) and were much higher than those for the open-ring metabolite. As noted in Figure 1, the PK population comprised 13 subjects as 2 subjects had insufficient data for the calculation of PK parameters. One subject had only 1 quantifiable concentration for each analyte, and a second subject had 2 quantifiable concentrations for ceftobiprole, 1 quantifiable concentration for ceftobiprole medocaril, and 2 quantifiable concentrations for the open-ring metabolite.

Summary statistics for the PK parameters for subjects enrolled in Study BPR-PIP-001 are presented in Table 1. Data for the 2 subjects with insufficient observed PK data mentioned above were excluded from the noncompartmental analysis. As expected, T_{max} for ceftobiprole occurred at 4 hours in all subjects and the median C_{max} was highest for ceftobiprole (11.2 μg/mL) compared with ceftobiprole medocaril (0.107 μg/mL) and the open-ring metabolite (0.644 μg/mL). Minimal accumulation of ceftobiprole would be expected with multiple dosing given that $AUC_{0\text{-inf}}$ was only about 10% larger than $AUC_{0\text{-last}}$ for ceftobiprole. This is consistent with the short terminal $T_{1/2}$ for ceftobiprole (median of 2.86 h). The $T_{1/2}$ for the open-ring metabolite was slightly longer (median of 5.30 h), which resulted in a larger difference between $AUC_{0\text{-inf}}$ and $AUC_{0\text{-last}}$. Approximately 44% of the administered

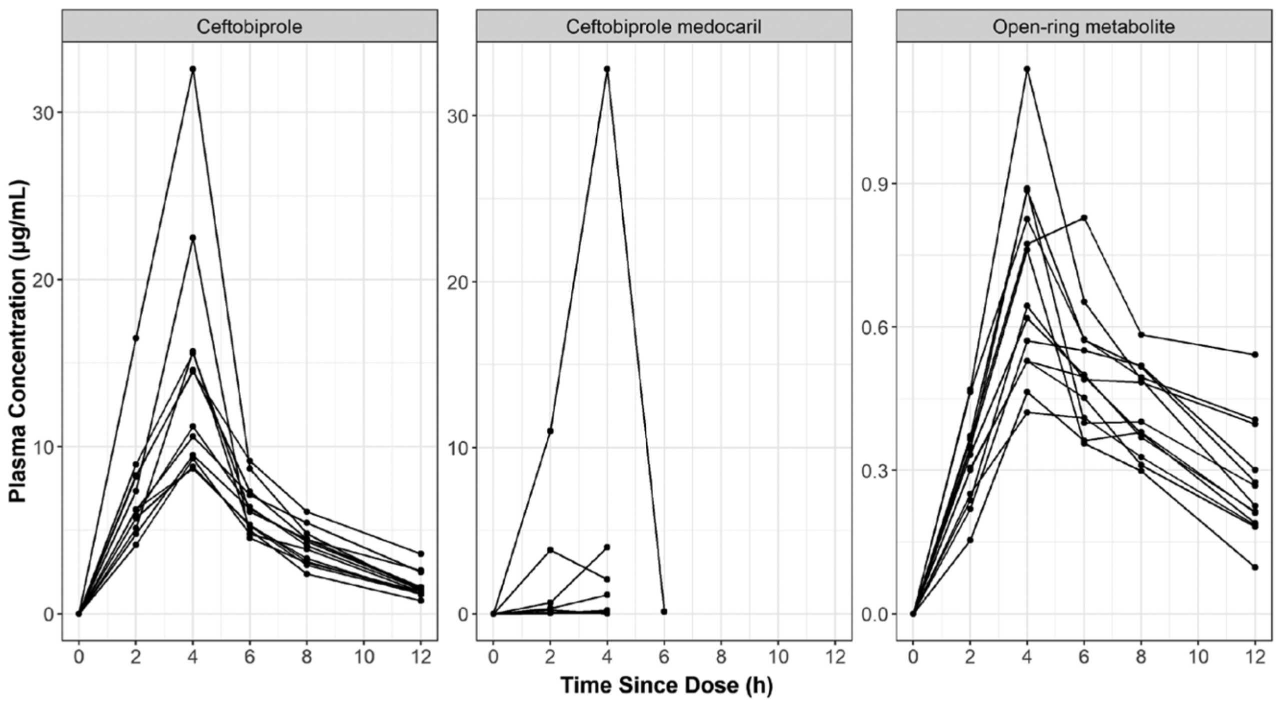

FIGURE 1. Observed plasma concentration-time profiles for neonates and infants up to 3 months of age (Study BPR-PIP-001, n = 13). h indicates hours; µg, micrograms; mL, milliliters.

TABLE 1. Summary Statistics for PK Parameters From the Single-dose Study in Neonates and Infants up to 3 Months of Age (BPR-PIP-001) Derived Using Noncompartmental Methods

PK Parameter	Ceftobiprole N	Ceftobiprole Median (Min–Max)	Ceftobiprole Medocaril N	Ceftobiprole Medocaril Median (Min–Max)	Open-ring Metabolite N	Open-ring Metabolite Median (Min–Max)
C_{max} (µg/mL)	13	11.2 (8.68–32.6)	13	0.107 (0.0149–32.8)	13	0.64 (0.421–1.14)
T_{max} (h)	13	4.00 (4.00–4.00)	13	4.00 (2.00–4.00)	13	4.00 (4.00–6.00)
AUC_{0-last} (µg•h/mL)	13	60.6 (49.1–126)	13	0.269 (0.0298–66.7)	13	4.80 (3.48–6.76)
AUC_{0-inf} (µg•h/mL)	13	66.6 (54.5–130)	–	–	13	6.76 (4.35–15.8)
$T_{1/2}$ (h)	13	2.86 (2.23–4.86)	–	–	13	5.30 (3.07–18.7)
CL (L/h/kg)	13	0.0766 (0.0411–0.995)	–	–	13	0.842 (0.380–1.28)
V_d (L/kg)	13	0.454 (0.191–0.616)	–	–	13	7.77 (5.00–10.8)
V_{SS} (L/kg)	13	0.480 (0.200–0.670)	–	–	13	8.62 (5.62–12.6)
Ae (% of dose)	13	35.9 (0.951–91.4)	13	0.685 (0–2.51)	13	3.04 (0.0280–7.26)
fT>MIC of 4 mg/L (h)*	13	5.40 (3.77–8.13)	–	–	–	–

*Calculated using free-drug concentrations.

Ae indicates percentage of administered dose excreted in the urine over the collection interval; AUC_{0-inf}, area under the plasma concentration-time curve from time zero to infinity; AUC_{0-last}, area under the plasma concentration-time curve from time zero to the last measured concentration; CL, oral clearance; C_{max}, maximum plasma concentration; CV%, percent coefficient of variation; fT>MIC, duration of time after dose for which free-drug concentrations remained above the minimum inhibitory concentration; h, hours; L, liters; mg, milligrams; Max, maximum; Min, minimum; mL, milliliters; µg, micrograms; N, number of observations or subjects; PK, pharmacokinetic; $T_{1/2}$, half life; T_{max}, time at which maximum concentration occurs; V_d, volume of distribution; V_{SS}, volume of distribution at steady state.

dose was excreted in the urine as ceftobiprole (~35–40%), open-ring metabolite (~3%), or ceftobiprole medocaril (<1%) over the 12-hour collection interval. Overall, calculated free-ceftobiprole concentrations remained above an MIC of 4 mg/L for a mean of 5.29 hours after the administration of a single dose. This would translate to a mean %fT>MIC of 66% of the dosing interval if the drug was given on an 8-hour schedule and 44% if the drug was given on a 12-hour schedule.

Study BPR-PIP-002

Plasma concentration-time data were available for 29 patients enrolled in Study BPR-PIP-002. Observed PK data stratified by 4 age groups (3 months to 1 year, 2–5 years, 6–11 years, and 12–17 years) for ceftobiprole, ceftobiprole medocaril, and open-ring metabolite are shown in Figure 2. Data from 5 patients were excluded from these figures for the following reasons: 2 patients had contamination of samples due to blood drawn from the infusion line, 2 patients had insufficient sample volume for the majority of samples, and 1 patient had samples provided as whole blood, which were not analyzable. Ceftobiprole peaked at the end of infusion (4 hours for infants and 2 hours for all other age groups). Concentrations of ceftobiprole medocaril and the open-ring metabolite were low overall.

Summary statistics for the ceftobiprole PK parameters, stratified by 4 age groups, are presented in Table 2. The corresponding tables for ceftobiprole medocaril and the open-ring metabolite are available in Tables, Supplemental Digital Content 1, http://links.lww.com/INF/E505, and Supplemental Digital Content 2, http://links.lww.com/INF/E506, respectively, and illustrate that exposure to these 2 analytes was substantially lower than that observed for ceftobiprole. Only 1 patient less than 2 years of age provided PK samples, thus limiting interpretation of any PK results in this youngest age group. In general, ceftobiprole exposure decreased with increasing age. The median C_{max} was highest for children 2–5 years of age (32.4 µg/mL) and lowest for adolescents 12–17 years of age (17.9 µg/mL). Similar trends were seen for AUC_{0-last} and AUC_{0-tau}. The trends seen in C_{max} and AUC across age groups are likely reflective of the lower doses used in the older age groups (adolescents received 10 mg/kg q8h, children 6–11 years of age received 15 mg/kg q8h, and children 2–5 years of age received 20 mg/kg q8h) as the estimated CL_{SS} is relatively consistent across age groups (albeit slightly lower in the adolescents). When normalized to body weight, ceftobiprole CL_{SS} was similar in children 2–5 years and children 6–11 years of age, while the adolescents exhibited lower CL_{SS}. Despite the differences in exposure and clearance, the terminal $T_{1/2}$ for ceftobiprole was similar across age groups with median values ranging from 1.90 to 2.10 hours. Consistent with the short $T_{1/2}$, the predicted $R_{accumulation}$ was low for all age groups (1.06–1.08). Calculated free-drug concentrations of ceftobiprole remained above an MIC of 4 mg/L on day 3 for a mean of 5.28 hours when dosed at 10 mg/kg in adolescents 12–17 years of age, 5.74 hours when dosed at 15 mg/kg in children 6–11 years of age, and 6.20 hours when dosed at 20 mg/kg in children 2–5 years of age. These values correspond to mean %fT > MIC values of 73.6%, 76.5%, and 83.7% of the 8-hour dosing interval, respectively. Overall, the %fT>MIC was slightly higher in younger children. The mean %fT>MIC values were 83.7% and 74.8% in children <6 years and those ≥6 years of age, respectively.

Safety

Baseline characteristics of the safety population in each study are presented in Table 3. A total of 15 term neonates (GA ≥37 weeks) were enrolled in Study BPR-PIP-001, all of whom were included in the safety population. Six patients (40%) reported 1 TEAE each. None of these TEAEs were determined to be drug related. Two TEAEs were classified as serious, including 1 (diaphragmatic hernia) that was considered severe. The patient with diaphragmatic hernia, who received ceftobiprole 16 days after birth, had a medical history of a congenital right diaphragmatic hernia repair 2 days after birth. The hernia that occurred during the study period was determined to be a recurrence and not related to study drug. This serious AE was reported as resolved. The second serious AE was a cerebral infarction that was mild in severity and occurred in a patient with meconium aspiration syndrome. At the last follow-up visit, the event was reported as resolving.

The remaining 4 patients with TEAEs included 2 patients who experienced mild diaper rash, 1 patient who experienced erythema of the hand, and 1 patient who experienced narcotic exposure with withdrawal. No deaths occurred during this study, and no AEs led to treatment discontinuation.

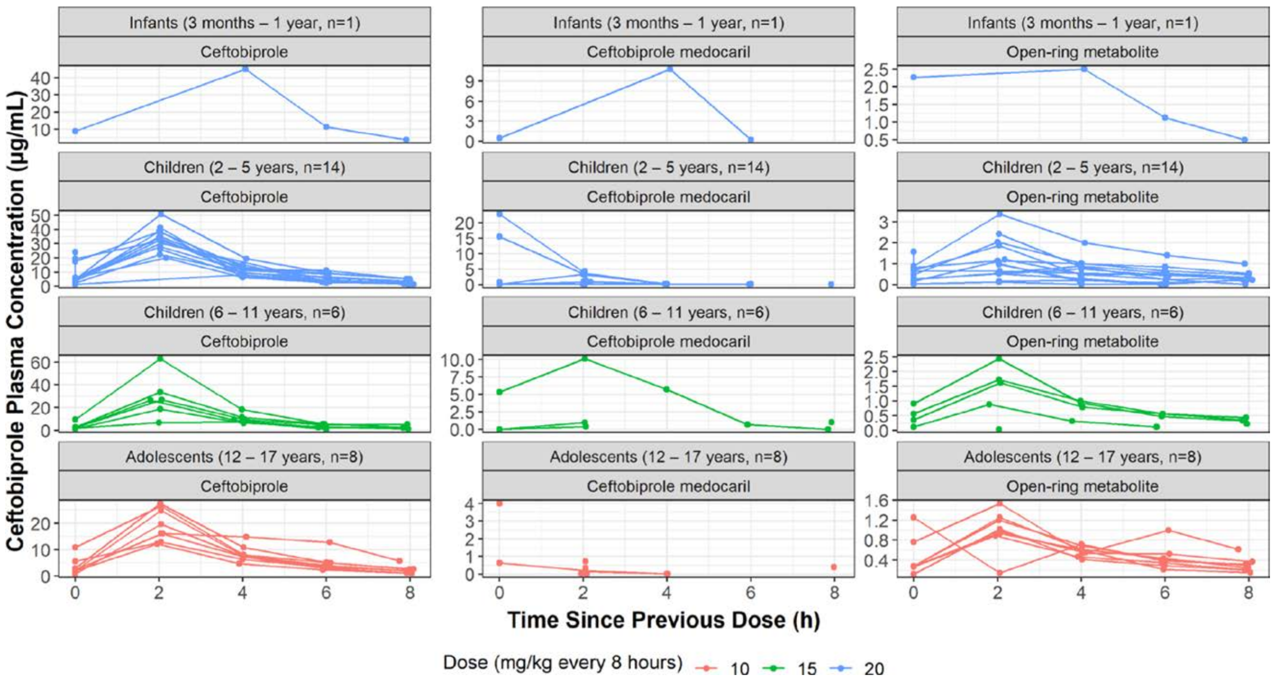

FIGURE 2. Observed ceftobiprole, ceftobiprole medocaril, and open-ring metabolite plasma concentration-time profiles for patients with pneumonia 3 months to 17 years of age (Study BPR-PIP-002). h indicates hours; kg, kilograms; μg, micrograms; mg, milligrams; mL, milliliters.

TABLE 2. Summary Statistics by Age Group for Ceftobiprole PK Parameters From the Study in Patients With Pneumonia 3 Months to 17 Years of Age (BPR-PIP-002) Derived Using Noncompartmental Methods*

	Children (2–5 y) 20 mg/kg IV Over 2 h		Children (6–11 y) 15 mg/kg IV Over 2 h		Adolescents (12–17 y) 10 mg/kg IV Over 2 h	
PK Parameter	N	Median (Min–Max)	N	Median (Min–Max)	N	Median (Min–Max)
C_{max} (μg/mL)	14	32.4 (20.0–50.8)	6	26.6 (7.44–62.8)	8	17.9 (12.1–27.4)
T_{max} (h)	14	2.03 (2.00–2.17)	6	2.03 (1.80–4.03)	8	2.05 (1.95–2.08)
$AUC_{0\text{-}last}$ (μg•h/mL)	14	106 (67.1–167)	6	83.4 (31.8–174)	8	68.1 (40.4–93.6)
$AUC_{0\text{-}tau}$ (μg•h/mL)†	14	106 (67.1–167)	6	83.4 (31.8–174)	8	68.1 (40.4–93.6)
$T_{1/2}$ (h)	14	2.10 (1.28–5.77)	6	1.90 (1.38–5.17)	8	2.02 (1.43–2.70)
CL_{SS} (L/h/kg)	14	0.147 (0.0930–0.231)	6	0.140 (0.0664–0.365)	8	0.113 (0.0618–0.192)
V_{SS} (L/kg)	14	0.462 (0.306–0.725)	6	0.460 (0.187–1.28)	8	0.365 (0.226–0.615)
$R_{accumulation}$	14	1.08 (1.01–1.62)	6	1.06 (1.02–1.52)	8	1.07 (1.02–1.15)
fT>MIC of 4 mg/L (h)‡	14	5.98 (3.32–8.01)	6	5.96 (3.58–7.79)	8	5.27 (3.12–7.52)
%fT>MIC of 4 mg/L‡	14	77.6 (61.2–100)	6	78.6 (50.8–98.1)	8	71.6 (52.7–96.6)

*There was only one patient in the 3 months to 1 year age group. The PK parameters for this patient are: C_{max}, 44.8 μg/mL; $AUC_{0\text{-}tau}$, 173 μg•h/mL; CL_{SS}, 0.900 L/h/kg; V_{SS}, 0.372 L/kg; and fT>MIC, 7.80 hours.

†Note that $AUC_{0\text{-}tau}$ is identical to $AUC_{0\text{-}last}$ for all patients as the time of the last observed concentration was within ± 15 minutes of 8 hours in each patient.

‡Calculated using free-drug concentrations.

$AUC_{0\text{-}last}$, area under the plasma concentration-time curve from time zero to the last measured concentration; $AUC_{0\text{-}tau}$, area under the plasma concentration-time curve from time zero to tau; CL_{SS}, oral clearance at steady state; C_{max}, maximum plasma concentration; CV%, percent coefficient of variation; fT>MIC, duration of time after dose for which free-drug concentrations remained above the minimum inhibitory concentration; %fT>MIC, percentage of the dosing interval for which free-drug concentrations remained above the minimum inhibitory concentration; h, hours; L, liters; mg, milligrams; Max, maximum; Min, minimum; mL, milliliters; μg, micrograms; N, number of observations or subjects; PK, pharmacokinetic; $R_{accumulation}$, accumulation ratio; $T_{1/2}$, half life; T_{max}, time at which maximum concentration occurs; V_{SS}, volume of distribution at steady state.

The results of the safety assessment for Study BPR-PIP-002 have been reported previously.[17] Ceftobiprole was generally well tolerated, with most AEs reported as mild or moderate in intensity. The most common AEs reported in this study were diarrhea, headache, and vomiting.

DISCUSSION

Plasma and urine concentration-time data collected from full-term neonates and infants enrolled in Study BPR-PIP-001 and pediatric patients 3 months to 17 years of age enrolled in Study BPR-PIP-002 allowed for characterization of the disposition of

TABLE 3. Baseline Characteristics in the Safety Populations of the Single-dose Study in Neonates and Infants up to 3 Months of Age (BPR-PIP-001) and the Study in Patients With Pneumonia 3 Months to 17 years of Age (BPR-PIP-002)

Study BPR-PIP-001		Study BPR-PIP-002		
Characteristic	Ceftobiprole N = 15	Characteristic	Ceftobiprole N = 94	Standard-of-care Cephalosporin N = 44
Sex, n (%)		**Sex, n (%)**		
Male	10 (66.7)	Male	53 (56.4)	21 (47.7)
Female	5 (33.3)	Female	41 (43.6)	23 (52.3)
Race, n (%)		**Race, n (%)**		
White	13 (86.7)	White	94 (100)	43 (97.7)
Black or African American	1 (6.70)	Black or African American	0	1 (2.30)
Native Hawaiian or Other Pacific Islander	1 (6.70)	Native Hawaiian or Other Pacific Islander	0	0
Gestational age (wks)		**Age (y)**		
Median (range)	39.4 (37.6–41.4)	Median (range)	5.00 (0.600–17.0)	6.00 (1.00–17.0)
Postnatal age (d)				
Median (range)	13.0 (5.00–67.0)			
Height (cm)		**Height (cm)**		
Median (range)	54.0 (49.0–61.0)	Median (range)	116 (71.0–184)	119.5 (77.0–175)
Weight (g)		**Weight (kg)**		
Median (range)	3980 (2500–5270)	Median (range)	20.0 (7.00–85.0)	19.8 (10.0–88.0)
BMI (kg/m²)		**BMI (kg/m²)**		
Median (range)	13.8 (10.0–15.6)	Median (range)	16.2 (8.80–32.8)	15.8 (12.8–28.7)

BMI indicates body mass index; cm, centimeters; g, grams; kg, kilograms; m, meters; N, number of observations or subjects.

ceftobiprole, ceftobiprole medocaril, and the open-ring metabolite in this population. Like in adults,[12] the prodrug (ceftobiprole medocaril) is rapidly converted to active ceftobiprole in the pediatric population with peak concentrations of ceftobiprole observed immediately after the end of the infusion. Exposure to ceftobiprole in plasma was demonstrated to be substantially higher than that for ceftobiprole medocaril and the open-ring metabolite. Consistent with this observation, the majority of drug recovered in urine from subjects enrolled in Study BPR-PIP-001 was in the form of ceftobiprole. As observed in adults (mean ± SD $T_{1/2}$ of 3.3 ± 0.3 hours),[4] the $T_{1/2}$ of ceftobiprole was short in the pediatric population with median values ranging from 1.90 hours in children 6–11 years of age to 2.86 hours in full-term neonates. The longer $T_{1/2}$ in neonates is likely secondary to immature renal function in this cohort.[22] Overall exposure to ceftobiprole in the pediatric patients (median AUC ranging from 66.6 to 173 µg•h/mL) was also similar to that observed in healthy adults receiving 500 mg q8h (mean ± SD of 102 ± 11.9 µg•h/mL).[4] The pediatric patients enrolled in Study BPR-PIP-002 exhibited faster CL_{SS} and larger V_{SS} than healthy, adult volunteers. The median CL_{SS} estimates ranged from 0.113 to 0.147 L/h/kg in pediatric patients 2 years of age or older in Study BPR-PIP-002 compared with 0.0721 L/h/kg for adults enrolled in a phase 1, multiple-dose study (assuming a mean body weight of 70 kg).[8] The median V_{SS} ranged from 0.365 to 0.462 L/kg in pediatric patients 2 years of age or older in Study BPR-PIP-002 compared with 0.239 L/kg for adults enrolled in the same phase 1, multiple-dose study.[8]

To assess the adequacy of drug concentrations in pediatric patients in terms of likely clinical efficacy, the fT > MIC for a nominal MIC value of 4 mg/L was evaluated using the observed ceftobiprole concentrations. This PK-PD index was chosen as the time that free-drug concentrations remain above the MIC of an infecting organism has been identified as the PK-PD driver for β-lactam antibiotics, including ceftobiprole.[13,14] The hypothetical MIC of 4 mg/L was considered a conservative target MIC given that it is the highest MIC_{90} value for ceftobiprole across relevant bacterial species.[23] The lowest observed %fT>MIC was 50.8%, which suggests that overall PK-PD target attainment can be expected to be sufficient in pediatric patients. Protein binding of ceftobiprole in this pediatric population was kept identical to the protein-binding estimate for the adult population (16%).[12] This was based on a relatively low protein binding of ceftobiprole in adults that is independent of drug concentration and the lack of available neonatal and pediatric data. For some other antibiotics, higher unbound drug fractions in neonates or children are observed compared with adults.[24–26] Therefore, the lack of measured free-drug concentrations is a limitation of this analysis and the %fT>MIC estimates from this analysis should be interpreted with caution.

The adequacy of expected PK-PD target attainment observed in the subjects that were enrolled in Study BPR-PIP-001 and Study BPR-PIP-002 should not be interpreted as full justification of the dosage regimens used in these 2 studies. First, the dose that was used for the neonates and infants enrolled in Study BPR-PIP-001 was selected specifically for the primary objective of that study (ie, to evaluate PK). To that end, a single dose of 7.5 mg/kg administered over 4 hours was used to ensure that the particularly vulnerable subjects enrolled in the study were not subjected to unnecessarily high ceftobiprole exposures given that there was no therapeutic intent for ceftobiprole. On the other hand, the doses used in Study BPR-PIP-002 were selected based on the fact that it was an efficacy study. Thus, higher doses were selected to ensure that subjects achieved ceftobiprole exposures that were associated with efficacy in adult phase 3 studies. While the doses used in Study BPR-PIP-002 were appropriate based on the clinical efficacy results of the study,[17] less complex dosing regimens with consistent infusion durations across age categories could theoretically provide similarly appropriate ceftobiprole exposures. A thorough examination of such alternative dosing regimens is outside the scope of this analysis.

Rational use of antibiotics in pediatric patients requires a thorough examination of not only the safety and efficacy but also the PK in this population. The results of the PK analyses provide important information in that regard. However, the use of noncompartmental methods for evaluating the PK has limitations in terms of the precision of the resultant PK parameter estimates (due to the relative sparseness of the PK sampling schemes) and the quantification of the variability in ceftobiprole PK in children and factors that drive that variability. Use of population PK modeling techniques have the potential to address these issues.[14] To that end, future analyses utilizing modeling and simulation approaches to more fully explore ceftobiprole dosing regimens that are most likely to be safe and effective in children are warranted.

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