Multiple Dose Pharmacokinetics of Ciprofloxacin in Preterm Babies

Poonam Aggarwal, Sourabh Dutta, S.K. Garg* and Anil Narang

From the Division of Neonatology, Department of Pediatrics and Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012, India.*

Correspondence to: Dr. Sourabh Dutta, Assistant Professor, Division of Neonatology, Department of Pediatrics, PGIMER, Chandigarh 160 012, India.

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Background: *Ciprofloxacin is increasingly used in preterm neonates to treat multi-drug resistant infections, however the pharmacokinetics of this drug in preterm newborns is not well studied.* ***Objectives:*** *To determine the multi-dose pharmacokinetics of intravenous ciprofloxacin in preterm infants.* ***Design:*** *Prospective, cohort study.* ***Setting:*** *Level III Neonatal Intensive Care Unit in a tertiary Care hospital in North India.* ***Methods:*** *24 preterm neonates with age < 28 days, who received intravenous ciprofloxacin 10 mg/kg/dose 12 hourly for clinical and/or culture proven sepsis, were enrolled. Serum levels of ciprofloxacin were analyzed after first dose on day 1 and at the end of days 3 and 7.* ***Results:*** *Of 24 babies included in the study [mean gestation (SD) 32 wks (2.4 wks)], 3 died and 1 dropped out in the initial few days, leaving 20 patients whose data on serum ciprofloxacin were available. Peak values on days 1, 3 and 7 were [mean ± SEM] 2.3 ± 0.39 µg/mL, 3.0 ± 0.44 µg/mL and 2.7 ± 0.39 µg/mL respectively (P >0.05). Trough values on these days were 0.7 ± 0.14 µg/mL 0.8 ± 0.14 µg/mL and 1.0 ± 0.21 µg/mL respectively (P > 0.05). There were no differences between the <1500 g and > 1500 g sub-groups and the < 7 days and >7 days sub-groups with respect to the corresponding peak and trough values on days 1, 3 and 7. The 95% C.I. of serum concentrations were above the MIC90 for most Enterobacteriaceae species, however the lower bound of the 95% C.I. of the mean trough levels was lower than MIC90 for Pseudomonas aeruginosa and Staphylococcus aureus. No adverse effects were observed.* ***Conclusions:*** *Intravenous ciprofloxacin in a dose of 10 mg/kg/dose 12 hourly is an effective treatment of neonatal sepsis, but higher doses may be required for treating Staphylococcus aureus and Pseudomonas.*

Key words: *Ciprofloxacin, Pharmacokinetics, Preterm.*

NEONATAL sepsis is a major killer of newborn babies in India, both in the community setting and in hospital(1,2). Hospital acquired neonatal infections in India are primarily caused by *Klebsiella*, *Staphylococcus aureus* and *Escherichia coli*(2). The incidence of multi-drug resistant infections is on the rise with resistance rates to gentamycin, amikacin and cefotaxime among gram negative organisms being 78.6%, 78.55% and 35.6% respectively; and resistance rates to penicillin, ampicillin and amikacin among *Staphylococcus* strains being 89.3%, 91.7% and 42.3% respectively(3).

Ciprofloxacin is a valuable antibiotic in our armamentarium against multi-drug resistant neonatal sepsis. Although it was a matter of concern earlier, there are enough data available now to dispel the fear of cartilage toxicity in newborns following the use of ciprofloxacin(4-6). There are several reports of the successful use of ciprofloxacin in neonatal sepsis or meningitis(7-8).

However, there are few reports of the pharmacokinetics of intravenous ciprofloxacin in neonates. These are either case reports of individual patients or case series of small groups of patients(7,9-12). No

systematic attempt has been made to determine the time to achieve a steady state concentration, or the possibility of a cumulative effect of multiple doses on the serum levels. Drug pharmaco-kinetics in preterm babies differs from other age groups because of higher extracellular fluid volume, immature renal and hepatic functions at birth, and post-natal maturation of these organs. The relationship of birth weight and postnatal age with ciprofloxacin pharmacokinetics has also never been studied before.

We conducted a prospective study to evaluate the multiple dose pharmacokinetics of ciprofloxacin in preterm babies and to determine the effects of birth weight and post-natal age on the pharmacokinetics of this drug.

Subjects and Methods

The study was conducted over a one-and-half year period in the Neonatal Unit of a tertiary care hospital in Northern India. Twenty four consecutive preterm neonates (gestation <37 weeks), who received intravenous ciprofloxacin for the treatment of sepsis at chronological ages less than 28 days, were enrolled in the study. The decision to use ciprofloxacin was taken by the treating neonatologist based on culture sensitivity reports and the clinical condition of the baby. Informed consent was taken from the parents prior to enrollment in the study.

After enrolment into the study, details of baseline demographics, ongoing medications and infecting organisms were recorded. Ciprofloxacin was administered as an intravenous infusion in the dose of 10 mg/kg/dose 12 hourly. Venous blood samples (1 mL each) were drawn in plain tubes on day 1, 3 and 7 at 15 minutes after the previous dose (*i.e.* peak level) and again before the next scheduled dose (*i.e.*, trough level). On day 1, the sample for peak level was drawn after the first dose of ciprofloxacin. The sera were separated and stored at –20°C till they were analyzed. The level of ciprofloxacin was assayed by HPLC, using the modified method of Weber *et al*.(13) Waater's HPLC system, which was used for the assay, consisted of a Model U6K injector, Model 510 pump, Model 680 gradient controller, Model 481 Lambda Max UV detector and micropbondapak C-18 column. For the mobile phase 32.5% HPLC grade methanol and 0.8% tetrahydrofuran in phosphate buffer (67 mmol/L, pH 3.0) were used. Ultraviolet light at 277 nm and 0.01 AUFS absorbance units was used for detection. Peak heights were used for quantitation. External standards consisting of known amounts of ciprofloxacin (0.25 -8 µg) were spiked to obtain standard curves on each day of the assay. The values of each sample were derived using the standard curve obtained on that particular day.

The peak and trough levels on day 1, 3 and 7 were described by descriptive statistics, and they were compared between days using paired *t* test. We also compared the serum levels between the <1500 g and >1500 g sub-groups, between the <7 days and >7 days post-natal age sub-groups, and between the small for gestational age (SGA) and appropriate for gestational age (AGA) sub-groups.

During ciprofloxacin therapy the patients were monitored clinically for adverse effects - *e.g.*, anaphylaxis, seizures, local reactions and arthropathy. The following biochemical parameters were also monitored: blood urea, serum creatinine, transaminases, alkaline phosphatase, total serum proteins and total serum bilirubin.

To cover *Staphylococcus aureus*, a minimum trough concentration of 1 µg/mL is required. Assuming a mean trough concentration of 1.25 µg/mL from a previous

study, a 95% confidence interval with a minimum lower bound of 1 µg/mL and standardized width of 0.9, a sample size of 19 subjects would be required(9).

Results

Twenty four babies were included in the study. They had gestational ages ranging from 28 to 36 weeks [Mean (SD) = 32.0 (2.4)] and birth weights ranging from 765 to 2900 g [Mean (SD) = 1502.7 (465)]. Of these, 20 (83.3%) were male and 4 (26.7%) were female. Sixteen babies were AGA, whereas 8 were SGA. Five babies had suffered perinatal asphyxia.

Ciprofloxacin therapy was started between 3 and 25 days of life. Twelve babies had septicemia with no localization, 4 had meningitis, 4 had pneumonia, 1 had colitis, 2 had necrotizing enterocolitis and 1 had septic arthritis. Cultures were positive in 9 out of 24 cases (37.5%). These included 6 blood, 2 CSF and 1 stool culture. *Klebsiella pneumoniae* was isolated in 4 cases, *Enterobacter aeruginosa* in 2, and *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhimurium* in 1 each. These isolates were all multi-drug resistant, but sensitive to ciprofloxacin. Fifteen babies did not have a positive blood culture, but they had a clinical course highly suggestive of septicemia and they had not responded to a penicillin/ cephalosporin and an aminoglycoside combination.

Along with ciprofloxacin the following drugs were being simultaneously used: aminophylline in 7 cases (29.2%), cefotaxime in 4 cases (16.7%), netilmycin and amikacin in 3 cases each (12.5% each), ceftazidime and phenytoin in 2 cases each, and phenobarbitone, itraconazole and fluconazole in 1 case each.

Five patients died and 2 left midway through treatment against medical advice. Of these, 3 patients died and 1 patient left against advice during the initial few days of therapy with ciprofloxacin. Thus, the data regarding serum ciprofloxacin levels were incomplete in 4 patients, and only 20 patients were taken into consideration while analyzing further results.

There were no significant differences between the peak and trough concentrations of ciprofloxacin on days 1, 3 and 7 (*Table I*).

The peak and trough levels (mean ± SEM) in the less than 1500 grams versus the more than 1500 grams groups are compared in *Table II*. These differences were not statistically significant. Similar results were obtained when the neonates were stratified in accordance with gestation (<34 wks vs >34 wks), postnatal age (<7 days vs >7 days) (*Table III*)S and intrauterine growth status (SGA vs AGA).

None of the subjects had evidence of anaphylaxis, seizures, arthropathy, local reactions or derangement in renal or hepatic functions during therapy with ciprofloxacin. Seven babies received aminophylline and ciprofloxacin concomitantly and they did not develop any signs of aminophylline toxicity.

Discussion

We studied serum ciprofloxacin levels in 24 babies with gestational age varying from 28 to 36 weeks on day 1, 3 and 7 of therapy. The sample on the third day was taken to find out whether the steady state concentrations of the drug were achieved prior to day 3. The sample on the seventh day was taken to find out whether there was a cumulative effect of the drug with multiple dosing.

Ciprofloxacin is known to be rapidly bactericidal at concentrations close to the MIC_{90}. Ciprofloxacin has MIC_{90} of less than or equal to 0.38 µg/mL against all species of *Enterobacteriaceae*, *Hemophilus*, *Acineto-*

TABLE I–*Peak and Trough Serum Ciprofloxacin Concentrations.*

Day	Parameter	Peak level (µg/mL)	Trough level (µg/mL)
1	Mean ± S.E.(95%CI)	2.3±0.39 (1.5-3.1)	0.7±0.14 (0.4-1)
	Range	0.2 -6.8	0.0 -2.1
3	Mean±S.E. (95% CI)	3.0.±0.44 (2.1 -3.9)	0.8±0.14 (0.5-1.1)
	Range	0.1 -7.1	0.0 -2.1
7	Mean±S.E. (95% CI)	2.7±0.39 (1.9-3.5)	1.0±0.21 (0.6- 1.4)
	Range	0.5 -7.1	0.1 -3.5

P > 0.05.

TABLE II–*Ciprofloxacin Concentrations in Relation to Birth Weight.*

		<1500 g (n = 12)	≥ 1500 g (n = 8)
Peak day 1 (µg/mL)	Mean ± SE (95% CI)	2.3 ± 0.58 (1.2 - 3.4)	2.4 ± 0.5 (1.4 - 3.4)
	Range	0.2 - 6.8	0.2 - 4.3
Trough day 1 (µg/mL)	Mean ± SE (95% CI)	0.7 ± 0.22 (0.3 - 1.1)	0.6 ± 0.14 (0.3 - 0.9)
	Range	0.0 - 2.1	0.0 - 1.2
Peak day 3 (µg/mL)	Mean ± SE (95% CI)	2.4 ± 0.46 (1.5 - 3.3)	3.8 ± 0.81 (2.2 - 5.4)
	Range	0.5 - 5.2	0.1 - 7.1
Trough day 3 (µg/mL)	Mean ± SE (95% CI)	0.7 ± 0.16 (0.4 - 1)	1.0 ± 0.24 (0.5 - 1.5)
	Range	0.1 - 1.7	0.0 - 2.1
Peak day 7 (µg/mL)	Mean ± SE (95% CI)	2.4 ± 0.33 (1.8 - 3)	3.2 ± 0.85 (1.5 - 4.9)
	Range	0.5 - 4.7	0.5 - 7.1
Trough day 7 (µg/mL)	Mean ± SE (95% CI)	1.1 ± 0.33 (0.5 - 1.7)	0.7 ± 0.18 (0.3 - 1.1)
	Range	0.1 - 3.5	0.1 - 1.4

P > 0.05.

bacter, and *Neisseria* and 0.8 µg/mL against Pseudomonas, whereas the MIC_{90} against Staphylococcus is 1 to 1.2 µg/mL(14). The serum concentration profile of intra-venous ciprofloxacin is best characterized by a first-order 3-compartment open model(15). The efficacy of ciprofloxacin depends on the area under the concentration time curve (AUC) above the MIC_{90}. Since AUC above the MIC_{90} is a function of the duration for which the level remains elevated, it is important that trough levels of ciprofloxacin do not fall below the MIC_{90}. In order to draw an inference from our study and apply it to the general population, the lower limit of the 95% confidence interval (CI) of the trough value ought to be above the MIC_{90}.

In our study, the mean peak concentrations ranged from 2.3 to 3.0 µg/mL and mean trough levels ranged from 0.7 to 1.0 µg/mL. Steady state levels were reached from the first day, and

TABLE III–*Ciprofloxacin Concentrations in Relation to Post-natal Age of Starting Therapy.*

		≤7 days (n = 8)	> 7 days (n = 12)
Peak day 1 (µg/mL)	Mean ± SE (95% CI)	2.5 ± 0.79 (0.9 - 4.0)	2.2 ± 0.41 (1.4 - 3.0)
	Range	0.2 - 6.8	0.5 - 5.4
Trough day 1 (µg/mL)	Mean ± SE (95% CI)	0.7 ± 0.26 (0.2 - 1.2)	0.7 ± 0.17 (0.4 - 1.0)
	Range	0.0 - 2.1	0.0 - 1.9
Peak day 3 (µg/mL)	Mean ± SE (95% CI)	3.3 ± 0.75 (1.8 - 4.8)	2.8 ± 0.56 (1.7 - 3.9)
	Range	0.1 - 7.1	0.5 - 6.8
Trough day 3 (µg/mL)	Mean ± SE (95% CI)	1.0 ± 0.27 (0.5 - 1.5)	0.7 ± 0.14 (0.4-1)
	Range	0.0 - 2.1	0.1 - 1.4
Peak day 7 (µg/mL)	Mean ± SE (95% CI)	2.6 ± 0.56 (1.5 - 3.7)	2.8 ± 0.55 (1.7 - 3.9)
	Range	0.5 - 4.7	0.5 - 7.1
Trough day 7 (µg/mL)	Mean ± SE (95% CI)	1.1 ± 0.41 (0.3 - 1.9)	0.9 ± 0.24 (0.4 - 1.4)
	Range	0.1 - 3.5	0.1 - 3.1

All P > 0.05.

there was no evidence of a cumulative build-up of serum levels over a week's duration. The trough levels were above the MIC_{90} of most clinically important pathogens, except *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In the case of the latter two organisms, the peak values were adequate but the AUC above the MIC_{90} would be inadequate because the 95% CI of the mean trough values fell on either side of the MIC_{90}. Among those babies in whom an organism was isolated, the individual serum trough levels were higher than the MIC_{90} of the corresponding organism. Three patients, who died during the course of ciprofloxacin therapy, had incomplete data regarding serum levels. From whatever data was available, the serum levels were above the required MIC_{90} in all cases, suggesting that death was not related to inadequate drug levels.

Since the glomerular filtration rate of very low birth weight (VLBW) babies differs significantly from non-VLBW babies, we compared the serum levels in these 2 groups and found no statistical difference, suggesting that dose modification is not required based on birth weigh(16).

As hepatic cytochrome P_{450} system as well as renal glomerular and tubular functions mature with postnatal age, we compared the serum levels in those less than 7 days versus those more than 7 days of age, and found no difference in the serum levels of ciprofloxacin(16).

Bannon, *et al.*(9) while using ciprofloxacin in 6 preterms in an intravenous dose of 5 mg/kg/dose 12 hourly found that the mean peak concentration was 3.1 µg/mL (range 1.45 to 5.7 µg/mL) after the third dose and mean trough level was 1.25 µg/mL (range 0.04 to 2.6 µg/mL). The relatively higher concentrations despite lesser dose compared to our study may have been due to the lower gestational age range studied (24 to 29 weeks) compared to ours (28 to 36 weeks). Van den Oever ,*et al.* (7) reviewed the pharma-cokinetics of cipro-

Key Messages

- Intravenous ciprofloxacin in a dose of 10 mg/kg/dose 12 hourly is an effective treatment for neonatal sepsis due to most common organisms, however higher doses may be required for *Staphylococcus aureus* and *Pseudomonas aeruginosa.*
- Short term safety of this dose is documented.

floxacin in 7 preterm infants, less than 30 wks gestation, reported from various studies. Intravenous doses ranging from 4 to 40 mg/kg/day yielded adequate serum peak concentrations (0.98 to 5.7 µg/mL), but trough-to-peak ratio were high (median 32%), suggesting slow elimination in preterm babies. Goepp, *et al.*(11) studied a single infant with ventriculitis, who received 35 mg/kg/day of ciprofloxacin. The peak serum level was 11.6 µg/mL after the 6th dose, but the trough level (0.9 µg/mL) was similar to our study(11). Wessalowski, *et al.*(12) reported serum levels of 0.1 to 2.8 µg/mL in random serum samples drawn from one term neonate, who had a brain abscess(12).

On the basis of our study we conclude that intravenous ciprofloxacin given in a dose of 10 mg/kg/dose 12 hourly to premature newborn infants provides the requisite serum concentration to kill common gram negative pathogens encountered in the neonatal period. The dose is insufficient to kill *Staphylococcus aureus* and *Pseudomonas aeruginosa* effectively. The treatment of *Staphylococcus aureus* and *Pseudomonas aeruginosa* may require a higher total daily dose divided into shorter dosing intervals. This needs further research. Our study did not have sufficient power to conclude whether dose modification is required in babies weighing less than 1500 g though previous studies have suggested slower elimination of ciprofloxacin in preterms less than 30 wks of gestation.

Contributors: PA recruited subjects, collected the samples and analyzed data, SD drafted the manuscript and analyzed data. SKG determined the drug levels. AN conceptualized the idea for this study and designed the study. All authors approved the final manuscript. SD shall stand as guarantor for the study.

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