ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1992, p. 1086–1090
0066-4804/92/051086-05$02.00/0

Vol. 36, No. 5

Pharmacokinetics of Single-Dose Oral Ciprofloxacin in Infants and Small Children

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Received 24 September 1991/Accepted 25 February 1992

The pharmacokinetics of orally administered ciprofloxacin (CIP) was studied in seven infants aged 5 to 14 weeks and nine children aged 1 to 5 years, most of whom were *Salmonella* carriers. In each case, 15 mg of CIP per kg of body weight was given with water on an empty stomach, and timed serum samples were taken during the following 12 h. The elimination half-life of CIP was significantly ($P < 0.001$) longer in the infants (2.73 ± 0.28 h; mean ± standard deviation) than it was in the children (1.28 ± 0.52 h). The area under the serum CIP concentration-time curve (AUC) from time zero to infinity was 16.1 ± 7.4 mg · h · liter^{-1} among the infants and 5.3 ± 3.3 mg · h · liter^{-1} in the children ($P < 0.01$). No significant differences in the maximum concentration in serum, time to maximum concentration in serum, or absorption half-life were observed between the two groups. In contrast, the mean residence time was twofold longer in the infants (4.6 h) than it was in the children (2.4 h; $P < 0.001$). The findings suggest that elimination of CIP is particularly rapid in children who just have passed infancy; they may require doses at shorter time intervals than those required by infants or older children or adults. In general, an oral dose of 10 to 15 mg of CIP per kg three times daily seems appropriate for children aged 1 to 5 years.

Changes in the cartilage tissue of young animals of species (e.g., beagle puppies) that are sensitive to high doses of ciprofloxacin (CIP) and other quinolones have resulted in the view that quinolones should not be used in children (1). However, extensive use of narrow-spectrum quinolones, such as nalidixic, pipemidic, and oxolinic acids (6, 13) has not disclosed arthropathic problems in children, although those drugs also cause changes resembling those caused by the newer quinolones (9, 16, 23, 29, 30). Except for some anecdotal reports of arthralgia (2, 11), no cartilage damage was found in three retrospective studies investigating the use of nalidixic acid in children (1, 26).

Since children have received older quinolones for several years (for chronic urinary tract infections), it is likely that arthropathy would have been detected if humans are prone to this complication. A number of case reports of successful quinolone treatment in children without significant side reactions have been published (3, 4, 8, 10, 15, 17, 19, 25, 27, 31), and moreover, a study of 463 infants and children from 3 days to 17 years of age showed that the safety profile of CIP did not differ substantially from that in adults; specifically, no arthropathy was reported (18). Hence, many pediatricians are inclined toward the view that at least some of the new quinolones are appropriate for use in children, provided that the indications are well defined (1, 9, 27).

CIP was one of the first quinolones on the market, but despite more than 5 years of experience and use among adult patients, data on the use of CIP in children are scanty. Pharmacokinetic data for CIP in infants and children in the first months and years of life are almost nonexistent.

The lack of adequate information is a special problem in situations in which quinolone therapy would be a relevant option. Because we were faced with that situation, a study with oral CIP was performed among infants and children aged 0 to 5 years. The result was that the pharmacokinetic experience obtained from adults is not directly applicable to pediatric patients.

MATERIALS AND METHODS

Background. *Salmonella* infections are rare in Finland unless an individual has some form of contact with an endemic area. So was the case of *Salmonella panama* meningitis in a neonate whose grandparents had recently visited the Mediterranean region.

Despite a 3-week course of therapy with an antimicrobial agent (ampicillin most of the time) to which the strain was susceptible, meningitis relapsed after the symptomless neonate had been discharged from the local hospital. The child was moved to Children's Hospital, University of Helsinki, where *S. panama* was rediscovered in the cerebrospinal fluid and the feces.

Ceftriaxone was instituted, and again, the clinical response was excellent. Despite this, the child became a *Salmonella* carrier. Because eradication trials with trimethoprim-sulfamethoxazole proved unsuccessful, the question of whether CIP would be more effective was raised. The key problem was that the baby was not taken to the day-care center as long as he excreted salmonellae. Hence, the mother had to stay home, which, in turn, caused considerable economic and social problems for the family.

After thorough discussions between the mother and the clinicians in charge, a decision was made that a short course of CIP should be tried in the index case. The mother also agreed that a pharmacokinetic study to learn the appropriate doses of CIP that should be used in children in this age group was desirable. Because there were two other children in the same household (who did not excrete salmonellae) who were at risk of getting infected, it was agreed that one oral dose of

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CIP would be given to the two other children and that data on the pharmacokinetics of CIP in these two boys would be collected as well. The same approach was agreed to by the parents of five other children, two of whom suffered from cystic fibrosis (which does not significantly alter the pharmacokinetics of CIP [28]) and two of whom suffered from prolonged pneumonia; the fifth child had a neurogenic bladder caused by a congenital lumbosacral malformation and suffered from repeat urinary tract infections.

At the same time that these events were occurring in Helsinki, an exceptional episode broke out in Länsi-Pohja Central Hospital in the city of Kemi. Two neonates had loose stools and very mild general symptoms and signs. A spinal tap from one of the infants produced macroscopically clear cerebrospinal fluid which, surprisingly, grew *Salmonella java*. Although samples were collected from the mothers and personnel in the delivery room, the nursery, the neonatal ward, and the hospital kitchens, the origin of infection remained obscure. However, because no *S. java* strains had been isolated in Finland during the several months prior to the outbreak, a source from abroad was likely.

The babies were isolated promptly, and routine therapy with the penicillin-gentamicin combination was instituted. After meningitis was diagnosed, the treatment was replaced by ceftriaxone treatment. The infant recovered uneventfully, but salmonellae were not cleared from the infant's stools. Although special hygienic precautions were executed, eight other infants became infected and began to excrete salmonellae, but without systemic symptoms or signs of disease. Over the following weeks, the infection cleared spontaneously from only two babies. Thus, in all, eight infants continued to excrete *S. java*.

The outbreak caused much concern, and then caused even more concern because the strain was later isolated from two mothers, one father, and a 2-year-old sister, all of who were household contacts of the infected infants. Oral trimethoprim-sulfamethoxazole did not eradicate salmonellae; on the other hand, local resources did not permit parenteral treatment for all infants involved. The outbreak was widely publicized, and the social pressure reached the extent that overt psychiatric problems broke out in at least one family.

Under these extraordinary circumstances it was deemed ethical by several experts to try short CIP treatment for all *Salmonella* carriers, provided that the parents of all children agreed. Although the potential risks of CIP treatment were made clear to the parents, the parents of each child consented to the treatment. The parents also accepted serial blood sampling for a pharmacokinetic study with the reasoning that the data obtained would benefit other children potentially in need of CIP therapy.

Every effort possible was made to detect any adverse events caused by CIP. The drug was administered and the samples were collected in the hospital. After 1 day in the hospital ward, the infants were discharged and the treatment was continued at home. All patients were controlled repeatedly by their own pediatrician during the following 6 months.

One infant continued to excrete salmonellae at the age of 7 months (unpublished data). Because he was still not allowed to attend the day-care center, it was agreed that intravenous CIP would be instituted to stop the excretion of salmonellae. In this context a comparative oral versus intravenous study was performed by giving the first two doses of CIP 12 h apart per os, and then, after a 48-h drug-free period, another two doses of CIP were given intravenously 12 h apart. The same amount of CIP (15 mg/kg of body weight) was given in each case. The purpose of the approach was to study whether much higher concentrations were achieved in serum by the intravenous administration. The question was even more pertinent because the serum CIP concentration remained rather low after oral dosing in the same patient (patient 7) at 14 weeks of age.

Drug administration. Except for the one child to whom CIP was administered intravenously, 15 mg of CIP per kg was administered orally as a single dose in the morning. Since a mixture form was not available, the tablet was ground, and the individual doses were measured by the hospital pharmacist according to the body weights of the patients. The drug was taken with approximately 50 ml of water, and swallowing was confirmed by visual observation. Eating was allowed a couple of hours later.

Timed blood samples (15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, and 12 h after administration of the drug) were drawn from a venous catheter. Serum was separated and was immediately frozen. All patients were monitored for potential adverse reactions by a special nurse.

Assay. Serum CIP concentrations were determined at the Department of Bacteriology and Immunology, University of Helsinki, by a standard agar diffusion method (12). Oxoid antibiotic medium no. 2 (pH 7.2) was used as the test medium, and a clinical isolate of *Escherichia coli* (isolate 44/UH-DBI) was used as the test organism. Seven standard concentrations were used on each plate. The standards and samples were placed in wells. The size of the samples in a 6-mm-diameter well was 65 μl.

The coefficients of variation [coefficient of variation = (standard deviation/mean) × 100] on the plates (n = 11) at the low (0.06 mg/liter), middle (0.5 mg/liter), and high (5.0 mg/liter) concentrations of CIP were 5.8, 2.7, and 3.1%, respectively, with corresponding mean inhibition zones of 17.1 ± 1.0 mm (standard deviation [SD]), 26.3 ± 0.7 mm (SD), and 35.1 ± 1.1 mm (SD), respectively.

The regression lines (least-squares formula) were calculated by using the values of seven different standards. The mean deviations of the standard concentrations measured from the respective points were −4.4 ± 4.7% (SD), at the low concentration, 5.5 ± 5.8% (SD) at the middle concentration, and −7.6 ± 4.3% (SD) at the high concentration.

Pharmacokinetics. Drug absorption was characterized by determining the maximum concentration of CIP in serum (C_{max}), time to C_{max} (T_{max}), the half-life of absorption, and the areas under the serum CIP concentration-time curve from 0 to 12 h (AUC_{0-12}) and from 0 h to infinity ($AUC_{0-\infty}$). In addition, estimates of the mean residence time, and the elimination half-life were determined. The serum CIP concentration-time data were fitted by an open one-compartment model with a first-order absorption by least-squares analysis with the SIPHAR program (SIMED, Creteil, France).

RESULTS

The patients are characterized in Table 1. No reactions attributable to the drug were observed in any subject involved in the study. However, one infant was excluded from the pharmacokinetics analysis because of immediate vomiting after CIP ingestion. The individual and mean ± SD values of the pharmacokinetic indices are listed in Table 2. The serum CIP concentrations are presented in Fig. 1 and 2.

The pharmacokinetics of CIP in the infants differed considerably from those in the children (Table 2). The elimination half-life of CIP in infants (2.73 ± 0.28 h) was signifi-

TABLE 1. Patient characteristics

Patient no.	Sex[a]	Age	Weight (kg)	Diagnosis[b]
1	M	5 wk	4.5	SC
2	F	7 wk	5.2	SC
3	F	7 wk	4.8	SC
4	F	7 wk	6.0	SC (index case for cases 1 to 3, 5, and 6)
5	M	7 wk	4.1	SC
6	M	10 wk	6.6	SC
7	M	14 wk	7.1	SC (index case for cases 13 and 15)
8	F	12 mo	10.0	Neurogenic bladder
9	M	13 mo	12.0	SC
10	F	18 mo	11.3	SC
11[c]	M	18 mo	11.7	Pneumonia
12[c]	F	18 mo	8.3	Pneumonia
13	M	2 yr, 7 mo	12.3	HHC
14	M	2 yr, 10 mo	12.3	Cystic fibrosis
15	M	4 yr, 8 mo	17.3	HHC
16	F	5 yr, 3 mo	16.7	Cystic fibrosis

[a] M, male; F, female.
[b] SC, salmonella carrier (see text); HHC, household contact (see text).
[c] Patients 11 and 12 were twins.

cantly longer than that in children older than 1 year (1.28 ± 0.52 h; $P < 0.001$). The $AUC_{0-\infty}$ was not less than three times greater in the infants than it was in the children ($P < 0.01$). Furthermore, the mean residence time was about twofold longer in infants ($P < 0.001$).

In contrast, no differences in C_{max} or T_{max} were observed between the groups. In the two groups, C_{max} and T_{max} were 3.3 ± 1.3 and 2.1 ± 1.4 mg/liter and 1.18 ± 0.46 and 1.00 ± 0.25 h in infants and children, respectively (Table 2).

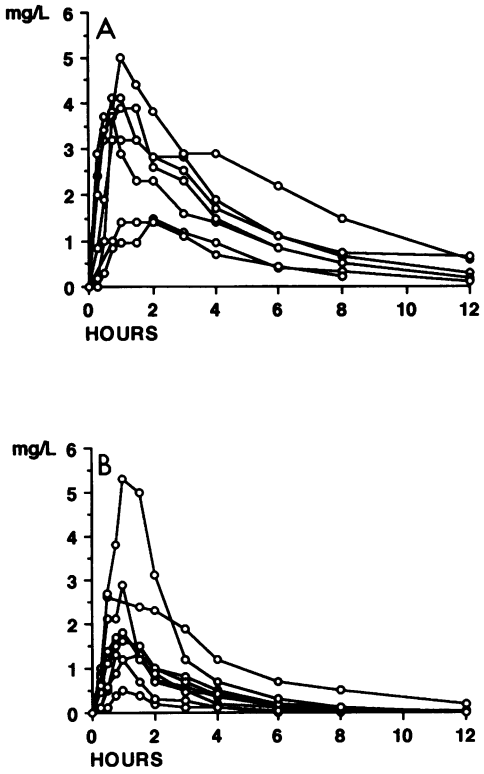

FIG. 1. Serum CIP concentrations in seven infants aged 5 to 14 weeks (A) and nine children aged 1 to 5 years (B) after ingestion of a single dose of 15 mg of ciprofloxacin per kg of body weight.

TABLE 2. Pharmacokinetic indices determined after an oral dose of 15 mg of ciprofloxacin per kg in the two study groups[a]

Age group and patient no.	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2\ abs}$ (h)	$t_{1/2\beta}$ (h)	$AUC_{0-\infty}$ (mg · h/liter)	MRT (h)
5–14 wk						
1	4.1	0.87	0.24	2.90	19.3	4.4
2	5.0	1.00	0.53	3.20	28.2	5.6
3	3.7	0.62	0.10	2.80	14.8	4.2
4	3.9	1.25	0.22	2.40	16.4	3.7
5	3.2	1.00	0.43	2.70	19.8	5.8
6	1.5	2.00	0.74	2.70	7.4	4.5
7	1.4	1.50	0.53	2.40	7.1	4.3
Mean ± SD	3.3 ± 1.3	1.18 ± 0.46	0.40 ± 0.22	2.73 ± 0.28	16.1 ± 7.4	4.6 ± 0.8
1–5 yr						
8	1.8	1.00	0.22	1.70	4.4	2.8
9	0.5	1.00	0.28	0.90	0.9	1.9
10	1.6	1.00	0.17	1.70	5.9	2.9
11	1.3	1.00	0.27	1.50	4.0	2.7
12	1.8	1.50	0.31	1.30	5.0	2.5
13	1.2	1.00	0.59	0.64	2.0	1.8
14	2.6	0.50	0.09	2.10	9.2	3.3
15	2.9	1.00	0.50	0.56	5.3	1.5
16	5.3	1.00	0.18	1.10	11.4	2.1
Mean ± SD	2.1 ± 1.7	1.00 ± 0.25	0.29 ± 0.16	1.28 ± 0.52	5.3 ± 3.3	2.4 ± 0.6
P value between the two groups	NS[b]	NS	NS	<0.001	<0.01	0.001

[a] C_{max}, maximum concentration in serum; T_{max}, time to maximum concentration in serum; $t_{1/2\ abs}$, half-life of absorption; $t_{1/2\beta}$, half-life of elimination; $AUC_{0-\infty}$, area under the concentration-time curve from 0 h to infinity; MRT, mean residence time.
[b] NS, not significant.

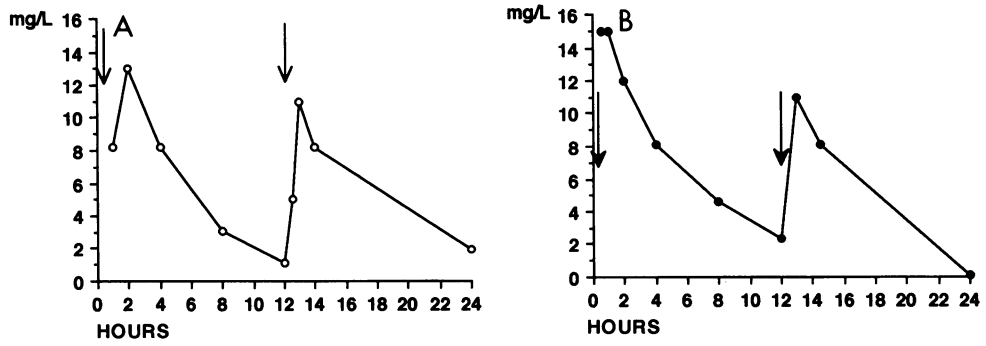

FIG. 2. Serum CIP concentrations in a 7-month-old child (patient 7) after oral administration of two doses of 15 mg of CIP per kg of body weight 12 h apart (A) and, after a 48-h drug-free period, another two doses of 15 mg of CIP per kg given intravenously 12 h apart (B). Arrows indicate the timing of drug administration.

The absolute bioavailability of CIP administered orally in a 7-month-old boy (weight, 9 kg) was 91% [(AUC_{oral}:$AUC_{intravenous}$) × 100]. As shown in Fig. 2, high concentrations of CIP were achieved in serum, regardless of whether the drug was administered orally (C_{max}, 13 and 11 mg/liter after the first and second doses, respectively) or intravenously (C_{max}, 15 and 11 mg/liter after the first and second doses, respectively). The same subject was tested 4 months earlier at the age of 14 weeks (patient 7). Then, after an oral dose of 15 mg/kg, the peak concentration of CIP in serum had remained as low as 1.4 mg/liter.

DISCUSSION

Because dose calculations of oral CIP in infants and small children have so far been based on arbitrary estimations derived from the experience in adults, there has been an urgent need for pharmacokinetic data for the pediatric population (24). Results of this study indicate that there are great differences between the pharmacokinetics of CIP in different age groups, even between infants and children (Table 2; Fig. 1A and B).

Before this study, age was not considered to play a major role in CIP dosing (7). Results of this study challenge that view. Although approximately equal peak concentrations are reached in serum with the same milligram-per-kilogram dosing in young infants and 1- to 5-year-old children, children seem to eliminate CIP much more rapidly than do infants or adults. In our study, the average elimination half-life in children in early infancy (2.7 h) was about twice that in the 1- to 5-year-old children (1.3 h).

Curiously, the elimination half-life in adults is 3.4 to 6.9 h (7), which is three to four times longer than that in children aged 1 to 5 years. Therefore, the age of the patient should be taken into account when CIP is prescribed. In this respect, the pharmacokinetics of CIP resembles that of trimethoprim, which is also eliminated more rapidly from children than it is from infants or adults (14). It is likely that one or more of the three routes of elimination of CIP—renal excretion, transintestinal secretion, and metabolism (7)—are particularly active after the first year of life.

In adults, the bioavailability of CIP averages between 69 and 85% (5). Because concomitantly ingested milk may considerably reduce the absorption of CIP administered orally (21), CIP was given with water on an empty stomach. The bioavailability and the volume distribution of CIP could not be determined because, except for one case (Fig. 2), only oral administration of drug was used.

Surprisingly, high concentrations of CIP in serum and a high absolute bioavailability (91%) of CIP were observed in one infant (age, 7 months) (Fig. 2). This was in contrast to the very low concentration in the same patient (patient 7) 4 months earlier. The apparent discrepancy may be related to physiological changes or, for example, to alterations in the functions of the gastrointestinal tract caused by *Salmonella* spp. Since the absorption of CIP is liable to be affected by the ingestion of milk and some drugs, the possibility of unknown absorption interactions cannot be excluded.

To avoid potentially subtherapeutic concentrations in serum on the one hand and concentrations that are too high (22) on the other, CIP should be administered more frequently to children than it is to adults, i.e., at least three times daily. A dose of 10 to 15 mg/kg three or even four times daily might be needed to achieve concentrations in serum comparable to those achieved in the sera of adults when the recommended twice-daily dosing of 500 to 750 mg of CIP is used. Frequent dosing seems especially relevant to young children who have passed infancy (Table 2; Fig. 1B). Although our single-dose recommendation for children (10 to 15 mg/kg) is somewhat higher than that for adults (6 to 10 mg/kg), the doses still remain about one-fourth to one-eighth of the doses of 50 to 100 mg/kg that have caused erosions in young animal species that are sensitive to the drug (11).

Pharmacokinetic data do not justify the free use of CIP in infants and small children, especially because of new observations of the adverse effects of CIP that have been observed (20). However, there are situations in which this drug poses a good alternative to other antimicrobial agents. Sometimes, the use of CIP (or another quinolone) may save the life of an infant (4).

ACKNOWLEDGMENT

We are indebted to Liisa Herva, chief of the pediatric service of Länsi-Pohja Central Hospital, who negotiated with the parents and shared actively in making the difficult decisions demanded by the outbreak.

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