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Pharmacokinetics of Oral and Intravenous Ofloxacin in Children with Multidrug-Resistant Typhoid Fever

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The pharmacokinetics of oral and intravenous ofloxacin (7.5 mg · kg of body weight^{-1} given over 30 min) were studied in an open crossover study of 17 Vietnamese children, aged between 5 and 14 years, with acute uncomplicated typhoid fever. Following oral administration, the median (95% confidence interval [CI]) time to peak concentration of ofloxacin in serum (C_{max}) was 1.7 h (1.4 to 1.9 h) and the mean (95% CI) C_{max} was 5.5 mg · liter^{-1} (4.7 to 6.3 mg · liter^{-1}) compared with a C_{max} of 8.7 mg · liter^{-1} (7.6 to 9.7 mg · liter^{-1}) following the intravenous infusion. The median (95% CI) total apparent volume of distribution following the first intravenous dose, 1.35 liter · kg^{-1} (1.17 to 1.73 liter · kg^{-1}), was significantly larger than that following the second dose, 0.99 liter · kg^{-1} (0.86 to 1.17 liter · kg^{-1}; $P < 0.0005$), although the estimates for systemic clearance were similar: 0.255 liter · kg^{-1} h^{-1} (0.147 to 0.325 liter · kg^{-1} h^{-1}) compared with 0.172 liter · kg^{-1} h^{-1} (0.127 to 0.292 liter · kg^{-1} h^{-1}; $P = 0.14$). The mean residence times (95% CI) following intravenous and oral administration were similar: 5.24 h (4.84 to 6.58 h) and 6.24 h (5.32 to 7.85 h), respectively. The mean (95% CI) oral bioavailability was 91% (74 to 109%). The peak concentrations in serum were 10 to 100 times higher than the maximum MICs for ofloxacin against multidrug-resistant *Salmonella typhi* isolated in this area. Although the systemic clearance values were higher than those reported previously for adults, these data overall suggest that weight- or area-adjusted dose regimens for the treatment of typhoid in older children should be the same as those for adults.

Strains of *Salmonella typhi* resistant to all first-line antimicrobial agents (e.g., chloramphenicol, trimethoprim-sulfamethoxazole, and amoxicillin) are increasingly prevalent in tropical areas. Fortunately, the fluoroquinolone antibiotics remain highly effective in the treatment of multidrug-resistant enteric fever, even when given for as little as 3 days. Because of reports of quinolone-induced arthropathy in juvenile animals (3, 4, 16), the use of fluoroquinolones in children is considered contraindicated. However, studies of children with cystic fibrosis (5, 20, 21) and recently of children with enteric fever (2, 10) have revealed no evidence of bone or joint abnormalities, which suggests that this adverse effect may be species specific. In Vietnam, ofloxacin has been used extensively over the past 2 years for the treatment of multidrug-resistant typhoid both in children and in adults (17, 24, 24a), as there are no orally effective alternatives to the fluoroquinolones. There are relatively few data on the pharmacokinetic properties of the fluoroquinolones in children; we therefore studied the pharmacokinetics of oral and intravenous ofloxacin in children receiving short-course treatment for typhoid fever.

MATERIALS AND METHODS

Study site. The study was conducted in a special study area of the Paediatric Intensive Care Unit at the Centre for Tropical Diseases, Ho Chi Minh City, Vietnam, a referral center for infectious and tropical diseases from southern Vietnam.

Patients. Consecutive patients, aged between 5 and 14 years, who were admitted with acute, uncomplicated multidrug-resistant typhoid fever were recruited into this open, randomized crossover study. These patients were also included in a much larger comparison of 2 versus 3 days of ofloxacin (15 mg · kg of body weight^{-1} · day^{-1}) for the treatment of enteric fever (24a). All patients were febrile and were blood culture positive for *S. typhi* at the time of their inclusion. All were able to tolerate oral medication, but none had received previous treatment with any fluoroquinolone drugs. Fully informed consent was given by the parents or guardians before entry of the children into the study, and the details of the study were explained to the children. This study was approved by the Ethical and Scientific Committee of the Centre for Tropical Diseases.

Procedures. The children were all treated with ofloxacin (Oflocet; Roussel-UCLAF, Paris, France) and were randomized to receive either 7.5 mg · kg^{-1} orally followed by 7.5 mg · kg^{-1} intravenously 12 h later or the same dose intravenously and then orally. This dose of ofloxacin was chosen on the basis of a previous study of multidrug-resistant typhoid in the Mekong Delta region of Vietnam (17). Parenteral ofloxacin (5 mg · ml^{-1}) was given intravenously over 30 min with a constant-rate infusion pump (Perfusor; B. Braun, Melsungen, Germany) connected to a butterfly needle sited in a large vein in a different limb from that being used for sampling. A small (22-gauge) indwelling catheter attached to a two-way tap was inserted into a large antecubital vein, and patency was maintained with heparinized 5% glucose. One-milliliter blood samples were taken before and then 0.5, 1, 2, 4, 6, 9, and 12 h after each dose of ofloxacin. The serum was separated and stored at −70°C until assayed between 2 and 6 months later (ofloxacin levels remain stable in serum under these conditions of storage [unpublished observations]). The course of ofloxacin was completed by using the oral route of administration. Patients were questioned daily about possible bone or joint symptoms. Other management was at the discretion of the treating physicians and according to hospital guidelines.

Ofloxacin assay. Serum ofloxacin concentrations were determined by high-performance liquid chromatography (HPLC) (25). The stationary phase was Spherisorb 5 ODS II in a stainless steel column (250 by 4 mm; HPLC Technology, Macclesfield, United Kingdom) heated to 50°C in a column heater (model TCM; Waters-Millipore, Harrow, United Kingdom). Fluorescence (excitation

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wavelength, 310 nm; emission wavelength, 489 nm; model LC240 detector; Perkin-Elmer, Beaconsfield, United Kingdom) was used for detection. The mobile phase was 3.2 ml of phosphoric acid added to 50 ml of acetonitrile and 946 ml of deionized water. The pH of the solution was adjusted to 3.0 by the dropwise addition of tetrabutylammonium hydroxide. The flow rate was 2.0 ml · min^{-1}. The specimens were prepared by mixing equal volumes of serum and methanol. The samples were spun, and 20 μl of the supernatant was injected. Interassay reproducibility for a 5.0-mg · $liter^{-1}$ standard ofloxacin sample was 4.1%, and the intra-assay reproducibility was 2.9 to 5.6%. The limit of assay sensitivity was 0.08 mg · $liter^{-1}$.

Pharmacokinetic analysis. Pharmacokinetic data were analyzed with PCNON LIN V4.0 (SCI Software, Lexington, Ky.), and models were selected on the basis of the Akaike information criterion (26). Data for the intravenous route of administration best fitted a two-compartment, open model. Because of the relatively sparse sampling schedule, data for the oral route of administration best fitted a single-compartment model with first-order input, first-order output, and no lag time. Simulations were performed to look for possible drug accumulation with different dose regimens. For both sets of data, noncompartmental analysis was also performed; area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) values were calculated by the trapezoidal method (15), and the elimination phase rate constants (β) were estimated by using the algorithms described by Dunne (8). $AUC_{0-\infty}$ values following the second dose were calculated after stripping the estimated $AUC_{12-\infty}$ values following the first dose. Individual bioavailability was estimated from the ratio of oral to intravenous $AUC_{0-\infty}$.

Statistical analysis. The distribution of data was assessed for normality by using the Shapiro-Wilks test. Normally distributed variables were expressed as means with 95% confidence intervals (CIs); results which were not normally distributed were expressed as medians with exact binomial 95% CIs. Differences between groups were assessed by using unpaired *t* tests for normally distributed results and the Kruskal-Wallis test for nonnormally distributed results. Differences among patients were compared by using paired *t* tests if the results were normally distributed and the Wilcoxon signed-rank test for matched pairs if they were not. Two-way analysis of variance was used to determine the effects of the route and sequence of administration of ofloxacin on calculated pharmacokinetic parameters.

RESULTS

Between November 1993 and June 1994 17 patients aged between 5 and 14 years were recruited into the pharmacokinetic study. All were blood culture positive for *S. typhi*. Ten patients were randomized to receive intravenous ofloxacin followed by oral ofloxacin ("i.v.-first" group), and seven patients were randomized to receive oral ofloxacin followed by intravenous ofloxacin ("i.v.-second" group). For one patient in the i.v.-first group, intravenous access was difficult and the pharmacokinetic study was abandoned before the second (oral) dose of the drug was given. The two groups were well matched in terms of age, sex, weight, height, and fever duration prior to hospital admission. The overall mean (95% CI, range) age in this study was 10.6 years (9.0 to 12.1 years, 5 to 14 years); the overall mean weight was 24.5 kg (21.0 to 28.0 kg, 17.0 to 34.0 kg); and the overall mean duration of fever before admission to the hospital was 12.2 days (9.5 to 14.8 days, 5 to 24 days). Both oral and intravenous ofloxacin were well tolerated, and no patient had to discontinue treatment because of adverse effects. Two patients receiving intravenous ofloxacin developed a superficial, nontender phlebitis along the course of the forearm vein into which the drug was infused, but this cleared quickly once the infusion had stopped.

Pharmacokinetics. Table 1 shows the pharmacokinetic parameters for the i.v.-first group and the i.v.-second group, obtained by using a two-compartment model. The mean (95% CI) maximum concentration of ofloxacin in serum (C_{max}) was lower in the i.v.-first group than in the i.v.-second group (8.6 mg · $liter^{-1}$ [7.3 to 9.8 mg · $liter^{-1}$] and 10.2 mg · $liter^{-1}$ [8.4 to 12.0 mg · $liter^{-1}$], respectively), but the difference was not significant ($P = 0.08$). The median (95% CI) steady-state total apparent volume of distribution was 1.35 liter · kg^{-1} (1.17 to 1.73 liter · kg^{-1}) for the i.v.-first group, compared with 0.99 liter · kg^{-1} (0.86 to 1.17 liter · kg^{-1}) for the i.v.-second group ($P < 0.0005$). The AUC_{0-12} was significantly greater for the i.v.-second group ($P = 0.019$), but the model-independent es-

TABLE 1. Pharmacokinetic parameters for ofloxacin given intravenously[a]

Group	C_{max} (mg/liter)[b]	V_{cc} (liter/kg)[c]	V_{ss} (liter/kg)[c]	AUC_{0-12} (mg · h · $liter^{-1}$)[b]	k_{10} (h^{-1})[b]	k_{12} (h^{-1})[c]	k_{21} (h^{-1})[b]	α (h^{-1})[c]	β (h^{-1})[b]	$t_{1/2\alpha}$ (h)[b]	$t_{1/2\beta}$ (h)[b]
i.v. first ($n = 10$)	8.55	0.625	1.35	25.84	0.445	1.08	1.07	2.23	0.170	0.315	4.32
	(7.34–9.77)	(0.474–0.707)	(1.17–1.73)[d]	(21.13–30.56)[e]	(0.317–0.572)	(0.58–1.92)	(0.636–1.51)	(1.42–3.50)	(0.140–0.200)	(0.209–0.420)	(3.37–5.27)
i.v. second ($n = 7$)	10.20	0.563	0.993	39.10	0.299	1.16	1.51	2.47	0.159	0.292	4.63
	(8.37–12.02)	(0.446–0.740)	(0.855–1.165)	(31.72–46.47)	(0.215–0.383)	(0.56–2.00)	(0.618–2.41)	(1.53–5.15)	(0.113–0.205)	(0.167–0.416)	(3.39–5.87)
Total ($n = 17$)	9.21	0.587	1.17	31.15	0.387	1.08	1.25	2.23	0.165	0.305	4.45
	(8.22–10.20)	(0.481–0.690)	(1.05–1.36)	(26.06–36.23)	(0.302–0.471)	(0.66–1.40)	(0.86–1.64)	(2.00–3.04)	(0.143–0.188)	(0.236–0.375)	(3.79–5.10)

[a] The dose was 7.5 mg · kg^{-1} given over 30 min. A two-compartment model was used for the calculations. V_{cc}, apparent volume of the central compartment; V_{ss}, volume of distribution at steady state; k_{10}, elimination rate constant from the central compartment; k_{12} and k_{21}, intercompartment rate constants; α, distribution phase.

[b] Values are means (95% CIs).

[c] Values are medians (95% CIs).

[d] $P = 0.0032$ by the Kruskall-Wallis test.

[e] $P = 0.019$ by the unpaired *t* test.

timates of systemic clearance were not significantly different: median (95% CI), 0.255 liter · kg^{-1} h^{-1} (0.147 to 0.325 liter · kg^{-1} h^{-1}) for the i.v.-first group, compared with 0.172 liter · kg^{-1} h^{-1} (0.127 to 0.292 liter · kg^{-1} h^{-1}) for the i.v.-second group ($P = 0.14$). There were no significant differences between the two intravenous groups in the other derived pharmacokinetic parameters. Simulations of these data revealed no significant accumulation of ofloxacin after the first day of treatment with repeated doses 12 h apart, even at a dose of 10 mg · kg^{-1} given for 7 to 10 days.

Table 2 shows parameters derived by using a single-compartment model from the two oral ofloxacin profiles, oral ofloxacin given first and oral ofloxacin given second. The AUC_{0-12} was higher when oral ofloxacin was given second than when it was given first, but the difference was not significant ($P = 0.06$).

A graph of the concentration of ofloxacin in serum versus time for all four dose profiles is presented in Fig. 1.

Two-way analysis of variance was used to assess differences in calculated model-independent pharmacokinetic parameters arising from the sequence of the route of administration and the route of administration itself. The order (orally first or intravenously first) in which ofloxacin was given had no effect on time to maximum concentration of ofloxacin in serum (T_{max}), C_{max}, β, half-life ($t_{1/2\beta}$), AUC_{0-12}, $AUC_{0-\infty}$, mean residence time from 0 to 12 h (MRT_{0-12}), $MRT_{0-\infty}$, or clearance estimates. The derived pharmacokinetic parameters were generally similar following oral and intravenous administration of ofloxacin, although the patients had a significantly higher mean C_{max}s and lower MRT_{0-12}s after receiving intravenous ofloxacin than after receiving oral ofloxacin ($P < 0.0001$ in both cases).

The results of a model-independent comparison of combined intravenous-administration results and combined oral-administration results are shown in Table 3. The mean (95% CI) C_{max} was significantly higher for intravenous administration (8.7 mg · $liter^{-1}$ [7.6 to 9.7 mg · $liter^{-1}$]) than for oral administration (5.5 mg · $liter^{-1}$ [4.7 to 6.3 mg · $liter^{-1}$]) ($P = 0.0008$), while the MRT was slightly shorter. The estimated acute bioavailability of oral ofloxacin was 91% (lower 95% CI, 74.1%). After correction for the estimated fraction of drug absorbed, the systemic clearance estimates for the two routes of administration were almost identical.

TABLE 2. Pharmacokinetic parameters for ofloxacin given orally[a]

Group	C_{max} (mg/liter)[b]	T_{max} (h)[c]	k_{01} (h^{-1})[c]	k_{10} (h^{-1})[b]	k_{01} half-life (h)[c]	k_{10} half-life (h)[b]	AUC_{0-12} (mg · h · liter)[b]	V/F (liter/kg)[b]
Oral first ($n = 7$)	5.53	1.52	2.17	0.280	0.320	2.83	23.3	1.20
	(3.50–7.55)	(0.70–2.19)	(0.76–12.72)	(0.178–0.381)	(0.056–0.937)	(1.80–3.86)	(21.7–25.0)	(0.87–1.54)[d]
Oral second ($n = 9$)	5.89	1.36	5.33	0.215	0.130	3.47	29.3	1.12
	(5.04–6.73)	(0.75–2.04)	(1.02–13.46)	(0.166–0.264)	(0.052–0.709)	(2.68–4.27)	(27.3–34.0)	(0.97–1.26)
Total ($n = 16$)	5.73	1.39	2.48	0.243	0.280	3.26	26.5	1.15
	(4.87–6.59)	(0.77–2.05)	(1.04–9.13)	(0.196–0.291)	(0.076–0.668)	(2.31–3.75)	(25.0–28.0)	(1.01–1.30)

[a] The dose was 7.5 mg/kg. A single-compartment model was used for the calculations. k_{01} and k_{10}, first-order absorption and elimination rate constants, respectively; V, volume of distribution; F, fraction of drug absorbed.
[b] Values are means (95% CIs).
[c] Values are medians (95% CIs).
[d] $P = 0.044$ by the unpaired t test.

DISCUSSION

The emergence of multidrug-resistant strains of *S. typhi* in many parts of the developing world has led to a reappraisal of the use of fluoroquinolones in children in situations in which no orally effective alternatives exist (19). Although data for juvenile animals suggest that these drugs damage cartilage (3, 4, 16), this has never been confirmed in humans, and studies with pediatric patients with cystic fibrosis (5, 19–21) and typhoid (2, 10, 24a) suggest that these drugs are highly effective and well tolerated and have no short- or long-term adverse effects. There is increasing acceptance that the fluoroquinolones should be used in the treatment of childhood infections when other safe and effective alternatives are not available or do not exist.

This is the first study of the pharmacokinetic properties of ofloxacin in children. The C_{max}s and profiles for concentration in serum versus time in this study are similar to those obtained for healthy adult volunteers after a single oral dose or intravenous infusion of between 600 and 800 mg (equivalent to approximately 10 mg · kg^{-1}) (6, 12, 18). The ofloxacin MIC at which 90% of the isolates are inhibited for Vietnamese strains of multidrug-resistant *S. typhi* at the time of this study was 0.06

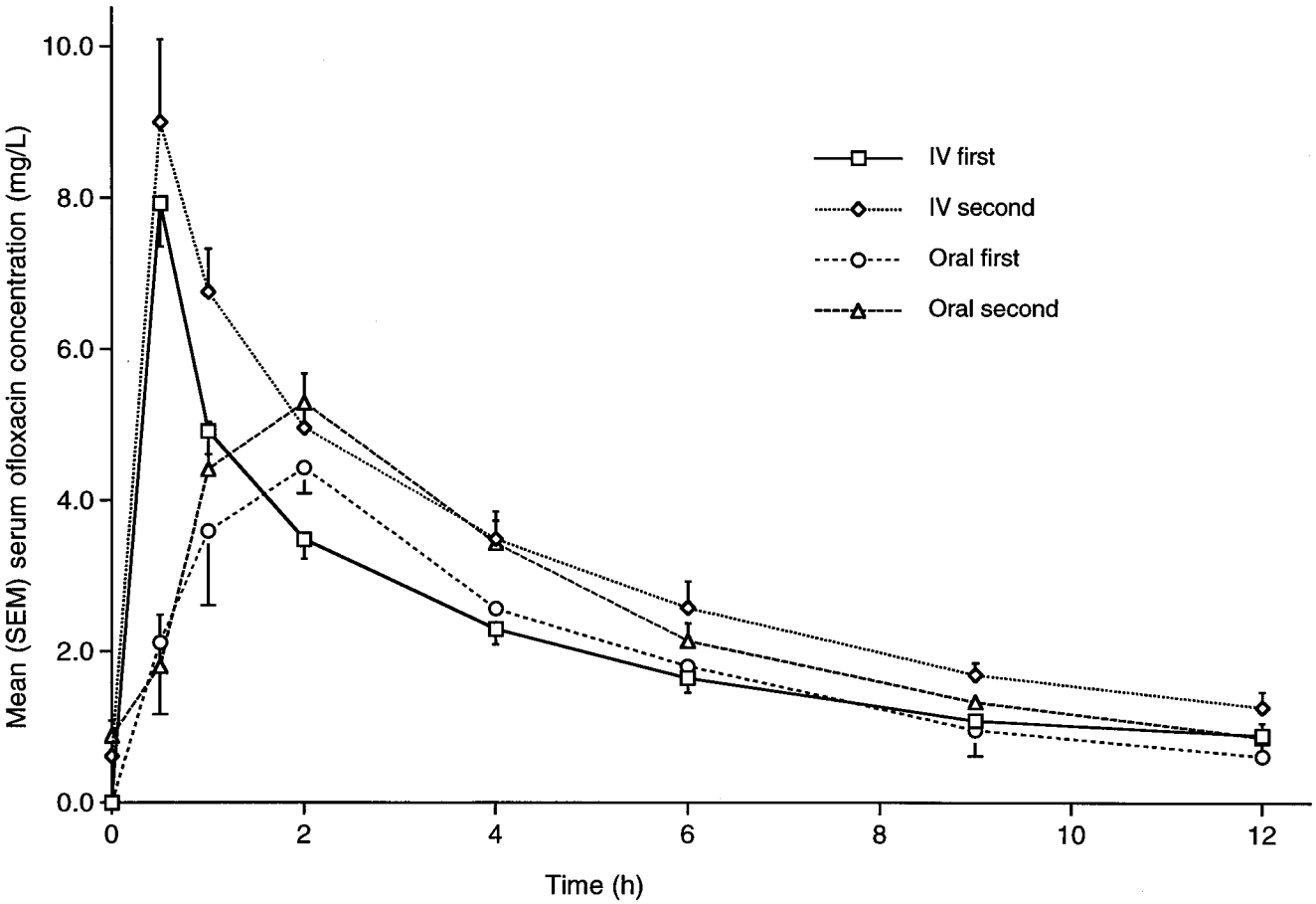

FIG. 1. Mean serum ofloxacin levels after oral and intravenous administration of 7.5 mg/kg. SEM, standard error of the mean.

mg · liter^{-1}, with a range of 0.06 to 0.5 mg · liter^{-1}. The ratio of the C_{max} (7) or AUC to the MIC for the infecting organism (13) is probably the most important determinant of fluoroquinolone efficacy. In children the C_{max}-to-MIC ratio for ofloxacin against multidrug-resistant *S. typhi* in this area ranges from approximately 10 to >100 (90% of cases are ≥100). C_{max}s were 60 to 100% higher following intravenous administration than they were following oral administration, but $AUC_{0-\infty}$ estimates were similar. This difference in C_{max}s for the two routes of administration therefore reflects incomplete distribution during the 30-min intravenous infusion. Concentrations in plasma would be expected to exceed 0.5 mg · liter^{-1} for approximately 18 h after a single ofloxacin dose of 7.5 mg · kg^{-1} in children with acute typhoid fever. Although the T_{max} after oral administration, $t_{1/2\beta}$, and volume of distribution calculated in this study were similar to those reported previously for adult volunteers, systemic clearance was more rapid (11, 12, 22). Children clear many drugs more quickly than adults (15). The elimination half-life of ofloxacin in young adults (mean age, 27 years) was shorter than that in older adults (mean age, 75 years) (18).

The effects of a disease on the pharmacokinetic properties of the drug used for its treatment are of obvious importance in determining dose regimens. As there are no previous data for patients with typhoid fever, or for children, it is not possible to distinguish the effects of age and disease on the pharmacokinetics of ofloxacin. Fever is known to increase the half-life and reduce the clearance of drugs such as antipyrine (9, 14), suggesting an impairment of hepatic oxidative metabolism. For Nepalese patients with uncomplicated typhoid, studies of the pharmacokinetics of ceftriaxone showed lower mean $t_{1/2\beta}$ and AUC values and higher mean total plasma clearance and volumes of distribution than in healthy volunteers given equivalent doses (1). Unlike ceftriaxone, which is eliminated mainly by biliary excretion, ofloxacin is excreted almost entirely unchanged by the kidneys. Patients with uncomplicated typhoid usually have normal creatinine clearances (23). Ofloxacin is 20% bound to plasma albumin, so any alterations in protein binding in our patients because of their prolonged bacterial illness are also unlikely to have had any significant effect on the disposition of the drug. Ofloxacin was also rapidly and completely absorbed. The mean oral bioavailability was 91%, with a lower 95% CI of 74%. These values are similar to those for healthy volunteers and indicate that the gastrointestinal pathology of enteric fever does not materially affect the absorption of ofloxacin. The estimates of apparent volume of distribution were larger after the first dose than after the second dose. This may reflect alterations in tissue distribution of the drug as the patients began to recover or may be an artifact resulting from incomplete correction for residual drug after the first dose or even from saturation of a "deep" tissue compartment. Apart from this there were small differences between the pharmacokinetic parameters estimated after the first and second doses and between oral and intravenous administration. Overall, these data suggest that a major effect of disease on ofloxacin disposition is very unlikely, that the oral

bioavailability of ofloxacin in patients with typhoid fever is excellent, and that dose regimens derived from studies with adults may also be applied to older children.

The dosage of ofloxacin used in this study was based on experience from an outbreak of multidrug-resistant typhoid in southern Vietnam, in which a 3-day course of ofloxacin at 7.5 $mg \cdot kg^{-1}$ twice daily was used successfully to treat over 200 patients, many of them children (17). In the present study, our patients were also randomized to receive ofloxacin for either 3 or 2 days of therapy; all were cured and none needed further antimicrobial treatment. Simulations suggested that significant ofloxacin accumulation would be very unlikely if the dose we used were to be given for longer periods of time.

In summary, ofloxacin at a dosage of 7.5 $mg \cdot kg^{-1}$ every 12 h given to children with typhoid fever was reliably absorbed, resulting in serum drug levels that were 10 to 100 times higher than the MIC for multidrug-resistant strains of *S. typhi* seen in Vietnam. On the basis of these data, a dose of 7.5 $mg \cdot kg^{-1}$ given orally every 12 h seems appropriate for the short-course treatment of enteric fever in children.

TABLE 3. Model-independent comparison of oral and intravenous ofloxacin[a]

Route of ofloxacin administration	C_{max} (mg/liter)[b]	T_{max} (h)[c]	β (h^{-1})[b]	$t_{1/2\beta}$ (h)[c]	$AUC_{0-\infty}$ ($mg \cdot h \cdot liter^{-1}$)[c]	$AUMC_{0-\infty}$ ($mg \cdot h^2 \cdot liter^{-1}$)[c]	$MRT_{0-\infty}$ (h)[c]	CL (liter $\cdot kg^{-1} \cdot h^{-1}$)[b]	V_{ss} (liter $\cdot kg^{-1}$)[b]	Bioavailability[b]
Intravenous infusion ($n = 17$)[d]	8.68 (7.61–9.74)[e]	0.50 (0.50–0.50)	0.159 (0.136–0.182)	4.42 (3.85–5.19)	34.13 (24.28–48.64)	200.3 (135.2–344.9)	5.24 (4.84–6.58)[f]	0.224 (0.183–0.265)	1.28 (1.12–1.44)	1
Oral ($n = 16$)[g]	5.46 (4.65–6.27)	1.69 (1.43–1.94)	0.151 (0.119–0.182)	4.33 (3.53–6.43)	32.32 (27.89–39.62)	218.8 (150.2–259.9)	6.24 (5.32–7.85)	0.242 (0.203–0.280)	NA	0.914 (0.741–1.087)

[a] AUMC, area under the first moment of the concentration-time curve from 0 to infinity; CL, clearance; V_{ss}, volume of distribution at steady state; NA, not applicable.
[b] Values are means (95% CIs).
[c] Values are medians (95% CIs).
[d] Dose, 7.5 mg/kg given over 30 min.
[e] $P = 0.0008$ by the paired t test.
[f] $P = 0.003$ by the Wilcoxon signed-rank test for matched pairs.
[g] Dose, 7.5 mg/kg.

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