ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1994, p. 2415–2418
0066-4804/94/$04.00+0

Vol. 38, No. 10

Pharmacokinetics of Ceftriaxone in Patients with Typhoid Fever

GOPAL ACHARYA,[1] CHARLES CREVOISIER,[2] THOMAS BUTLER,[3]* MAY HO,[4] M. TIWARI,[1] KLAUS STOECKEL,[2] AND CHARLES A. BRADLEY[3]

Teaching Hospital, Tribhuvan University, Kathmandu, Nepal[1]; F. Hoffmann-La Roche Ltd., CH-4002 Basel, Switzerland[2]; Departments of Internal Medicine and Pathology, Texas Tech University Health Sciences Center, Lubbock, Texas 79430[3]; and Department of Microbiology and Infectious Diseases, Calgary University, Calgary, Canada[4]

Received 30 August 1993/Returned for modification 20 January 1994/Accepted 14 July 1994

Ceftriaxone in short courses has emerged as an effective alternative to chloramphenicol for the treatment of typhoid fever. To study the pharmacokinetics of ceftriaxone in acute typhoid fever, 10 febrile Nepalese adolescents and young adults with blood culture-positive illness were treated with 3 g of ceftriaxone (intravenous infusion for 30 min) daily for 3 days. On the 1st and 3rd day of treatment, blood and urine samples were collected at defined intervals for measurements of drug concentrations. Kinetic parameters including concentrations at the end of infusion (C_{max}) and 24 h after the end of infusion (C_{min}), elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve (AUC), total plasma clearance, renal clearance, percentage excreted in urine, and volume of distribution were estimated. On day 1, mean values were as follows: C_{max}, 291 μg/ml; C_{min}, 21.7 μg/ml; plasma $t_{1/2}$, 5.2 h; AUC, 1,428 μg · h/ml; total plasma clearance, 37 ml/min; renal clearance, 19 ml/min; percentage excreted in urine, 49.7%; and volume of distribution, 16.1 liters. Mean values on day 3 were not significantly different from those on day 1. Compared with published values for healthy volunteers who received the same dose, our mean $t_{1/2}$s and AUCs were lower and our mean total plasma clearances, renal clearances, and volumes of distribution were higher. The good clinical responses of these patients to therapy and the adequate C_{min}s support the use of ceftriaxone once daily for the treatment of typhoid fever.

Chloramphenicol has remained the drug of choice for treating typhoid fever for more than 35 years because no newer antimicrobial drug has been shown to give better or more consistent clinical improvement at a comparable cost. In vitro resistance to chloramphenicol in *Salmonella typhi* occurs (5, 14) but has not become prevalent in most endemic areas of the world (6). Chloramphenicol, on the other hand, is not ideal treatment for typhoid fever because (i) treatment does not prevent fecal carriage of *S. typhi*, relapses after the end of therapy, or the complications of intestinal perforation and bleeding; (ii) a residual mortality occurs during therapy; (iii) reversible bone marrow suppression develops and rare aplastic anemia is a risk; and (iv) a long 14-day course of treatment requires dosing four times a day. Shorter courses of chloramphenicol are not advised because relapses occur in 10 to 20% of treated cases 1 to 2 weeks after the end of therapy.

Ceftriaxone is a newer cephalosporin antibiotic with good in vitro activity as shown by MICs of 0.05 μg/ml against most tested *Salmonella* strains (15). Its prolonged serum half-life ($t_{1/2}$) of 8 h and biliary excretion permit less-frequent administration of the drug to patients with enteric infections (2, 8, 9, 16). The use of ceftriaxone in mouse typhoid showed a good therapeutic effect (1), and an open trial with 14 patients with typhoid fever in Singapore produced cures in 13 patients (20). Randomized trials in Bangladesh using ceftriaxone once daily for 7 days (8) and in the Philippines once daily for 3 days (11) showed results comparable to those with chloramphenicol. In Taiwan, ceftriaxone was used daily for only 2 to 3 days and showed satisfactory results (4).

The pharmacokinetics of ceftriaxone have been reported from studies of healthy volunteers (2, 7, 9, 13). However, in patients with typhoid fever, the pharmacokinetics of antibiotics may be different from that of healthy controls because of fever (12) and transient dysfunction of liver or kidney (3) during their disease.

MATERIALS AND METHODS

Patient selection. Men and women between 14 and 28 years of age who presented to the outpatient clinic of Teaching Hospital in Kathmandu, Nepal, with a complaint of fever lasting more than 4 days were screened. Other features that were considered suggestive of the diagnosis of typhoid fever were headache, fatigue, splenomegaly, abdominal pain, and diarrhea. Blood cultures were made. Only patients with blood cultures positive for *S. typhi* or *S. paratyphi* A were included in the analysis of pharmacokinetics. Exclusion criteria were use of antimicrobial drugs within 2 weeks of presentation, pregnancy or lactation, allergy to penicillins or cephalosporins, and severe illness complicated by seizures, coma, pneumonia, intestinal hemorrhage, shock, or suspected intestinal perforation.

Therapy. Patients were hospitalized. Each patient received 3 g of ceftriaxone reconstituted in 100 ml of 5% dextrose in sterile water for intravenous infusion over 30 min. This dose was repeated twice at 24-h intervals for a total of three doses. No other medications were allowed. Adequate hydration was maintained by intravenous fluid as needed. Patients were permitted oral fluids and food ad libitum.

Clinical assessments. Patients were examined at least once daily. Vital signs were recorded three times a day. Blood cultures were repeated on day 4 of hospitalization. Specimens for stool cultures were taken before therapy and on day 7. Aliquots of plasma and urine were used for chemical determinations and calculation of creatinine clearance (CL).

* Corresponding author. Phone: (806) 743-3189. Fax: (806) 743-3148.

TABLE 1. Characteristics and laboratory values for 10 patients with typhoid fever before treatment

Characteristic	Mean value ± SD (range)	Normal ranges of laboratory values
Age (yr)	19.5 ± 4.3 (14–28)	
No. of males/no. of females	7/3	
Body wt (kg)	45.1 ± 7.3 (37–51)	
Height (cm)	160 ± 6 (152–168)	
Temp (°C)	38.9 ± 0.3 (38.0–39.0)	
Pulse rate/min	83 ± 2 (82–86)	
Blood pressure (mm Hg)		
Systolic	105 ± 5 (100–110)	
Diastolic	70 ± 5 (60–80)	
Days of illness before admission	5.8 ± 2.2 (3–10)	
No. with		
Abdominal pain	6	
Diarrhea	4	
Headache	10	
Splenomegaly	10	
Fever	10	
Delirium	1	
Hemoglobin (g/100 ml)	13.7 ± 0.8 (12.6–15.0)	12.0–17.5
No. of leukocytes/mm^3	7,640 ± 1,506 (5,000–10,000)	5,500–11,000
No. of platelets/mm^3 (1,000)	206 ± 42 (160–280)	150–450
Blood urea nitrogen (mg/dl)	14.7 ± 8.2 (5–30)	7–18
Creatinine (mg/dl)	0.79 ± 0.22 (0.5–1.1)	0.6–1.3
Creatinine CL (ml/min)	53.0 ± 13.4 (30.1–71.7)	80–139/1.73m^2
Aspartate aminotransferase (U/liter)	61.9 ± 31.2 (34–141)	10–30
Alanine aminotransferase (U/liter)	14.5 ± 4.5 (8–24)	8–20
Gamma-glutamyltransferase (U/liter)	36.3 ± 34.2 (10–100)	8–50
Bilirubin (mg/dl)	0.85 ± 0.22 (0.7–1.4)	0.2–1.0
Total protein (g/dl)	6.59 ± 0.53 (5.6–7.1)	6.4–8.3
Albumin (g/dl)	4.59 ± 0.59 (3.9–5.9)	3.5–5.0
Blood culture isolates		
No. of *S. typhi*	7	
No. of *S. paratyphi* A	3	

Blood and urine sampling for drug assays and pharmacokinetic analysis. Blood was drawn into Vacutainers containing potassium ammonium oxalate as anticoagulant at the following times (in hours) after drug infusion on days 1 and 3 of treatment: 0 (end of infusion), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24. Plasma was separated by centrifugation and stored at −20°C. Urine was collected completely at the following intervals (in hours): predose, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, and 12 to 24. The volume of each specimen was measured, and samples were stored at −20°C. Plasma and urine samples were transported with dry ice to F. Hoffmann-La Roche, Basel, Switzerland, for drug assays. The plasma and urine samples were analyzed by ion pair reversed-phase liquid chromatography using a UV detection at 274 nm (21). Quality control plasma specimens at concentrations of 20, 101, and 506 μg/ml (coefficients of variation of 3.4, 2.1, and 4.1%, respectively) and urine specimens at concentrations of 22, 67, 337, and 674 μg/ml (coefficients of variation of 3.9, 3.1, 1.2, and 0.8%, respectively) were analyzed in duplicate with each assay batch. Calibrations were linear from 5 to 500 μg/ml ($r^2 > 0.999$) and from 8 to 674 μg/ml ($r^2 > 0.999$) for plasma and urine, respectively. The quantitation limit was 5 μg/ml for plasma and 8 μg/ml for urine. Ceftriaxone plasma concentration-time data were analyzed by noncompartmental methods to determine terminal disposition rate constant (β), $t_{1/2}$, total plasma CL, and volume of distribution. The area under the plasma concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) was determined up to the last measured concentration by the linear trapezoidal rule and extrapolation from the last sampling time (t_n) to time infinity (last measured concentration/β). The parameter β was determined by linear regression analysis of the terminal part of the log-linear plasma $AUC_{0-\infty}$. The following equations were used:

$CL_{day\ 1}$ = dose/$AUC_{0-\infty}$; $CL_{day\ 3}$ = dose/AUC_{0-24}; $t_{1/2}$ = ln 2/β; and Volume of distribution = CL/β.

The renal CL (CL_R) was calculated by the equation $CL_R = U_{0-24}/AUC_{0-24}$, where U_{0-24} = amount of ceftriaxone excreted in urine within 24 h. The concentrations at the end of infusion (C_{max}) and 24 h thereafter (C_{min}) were taken directly from the observed concentration-time values. The pharmacokinetic parameters calculated on day 1 and day 3 were statistically compared by the nonparametric Wilcoxon test.

RESULTS

Characteristics of patients and laboratory results. Patients were young Nepalese who were predominantly males (Table 1). They had histories of acute febrile illnesses lasting for 3 to 10 days before admission. Most had illnesses of moderate severity, and none was judged to be severe or complicated. None gave histories of allergic reactions to penicillins or cephalosporins. Vital signs indicated that patients had elevated temperatures and normal pulse rates and blood pressures.

Laboratory tests showed hemoglobin values and leukocyte counts and platelets in the normal range. Tests of renal and hepatic function were also normal, except for a reduced mean of creatinine CL and an elevation of the mean of aspartate

TABLE 2. Pharmacokinetics of ceftriaxone in patients with typhoid fever

Parameter	Mean value[a]	
	Day 1	Day 3
C_{max} (μg/ml)	291 ± 92	298 ± 89
C_{min} (μg/ml)	21.7 ± 25.4	20.1 ± 11.2
$t_{1/2}$ (h)	5.2 ± 1.2	5.3 ± 1.3
$AUC_{0-\infty}$ (μg · h/ml)	1,428 ± 335	1,473 ± 394
Total plasma CL (ml/min)	37 ± 11	39 ± 11
CL_R (ml/min)	19 ± 9	18 ± 7
% Dose excreted in urine in 24 h	49.7 ± 9.8	43.8 ± 9.5
Vol of distribution (liters)	16.1 ± 3.3	17.0 ± 2.3

[a] Values are means ± standard deviations for 10 patients.

aminotransferase. Blood cultures were positive for *S. typhi* in seven patients and for *S. paratyphi* A in three patients.

Therapy and outcome. All patients received 3 g of ceftriaxone given as an intravenous infusion over 30 min once daily for 3 days. All patients improved clinically, with reductions in temperature and severity of symptoms, during a week or longer in the hospital. Temperatures, which were recorded three times a day, revealed that the time to defervescence (<37.8°C for at least 2 days) ranged from 2 to 8 days, with a mean of 4.0 days. There were no deaths or complications. Blood cultures on day 4 after the start of therapy were negative for *Salmonella* species in all cases. No patient returned with a clinical relapse after discharge.

Pharmacokinetics. Pharmacokinetic parameters showed no statistically significant differences ($P > 0.05$) between values on day 1 and day 3 of therapy (Table 2). The accumulation of ceftriaxone between day 1 and day 3 was negligible, as shown by the plasma concentration-time profile (Fig. 1).

DISCUSSION

The usefulness of ceftriaxone in once-a-day intravenous dosing for treatment of typhoid fever was confirmed in this study of 10 patients, who showed satisfactory clinical and bacteriologic responses after receiving 3 g/day for 3 days. The good clinical and bacteriologic responses correlated with attainment of trough concentrations of ceftriaxone in plasma (C_{min}) of greater than 11 μg/ml, which corresponds to approximately 0.5 μg/ml for the unbound concentration. These plasma concentrations exceeded manyfold the expected MICs for *Salmonella* strains, which are around 0.05 μg/ml (15).

It is of interest to compare the kinetic data for patients with typhoid fever with published data for healthy volunteers receiving the same intravenous dose (13). The kinetic parameters based on total plasma concentrations should be compared at the same dose level because of the concentration-dependent protein binding of ceftriaxone (7, 18). The total plasma CL in patients with typhoid fever was higher on day 1 and day 3 than in healthy volunteers (37 and 39, respectively, versus 18.5 ml/min) (13). As a result of the higher CL, the AUC was smaller for patients with typhoid fever (1,428 and 1,473, respectively, versus 2,725 μg · h/ml) (13). The elimination $t_{1/2}$ was shorter for patients with typhoid fever than for healthy volunteers (5.2 and 5.3, respectively, versus 8.0 h) despite a greater volume of distribution (16 and 17, respectively, versus 13 liters) (13). These data indicate that in patients with typhoid fever, ceftriaxone is more rapidly eliminated as a result of the higher systemic CL. The CL_R in our patients was also higher than in healthy volunteers (19 and 18, respectively, versus 12 ml/min) (13).

The possible explanations for greater CL_R and systemic CL and volume of distribution in patients with typhoid fever than in healthy volunteers include effects of fever (12), increased capillary permeability caused by systemic inflammatory reaction, and genetic factors. CL_R of ceftriaxone would be increased if protein binding of ceftriaxone was reduced in our patients because of hypoalbuminemia (19). A larger unbound fraction of ceftriaxone in plasma would result in increases of both the renal clearance and volume of distribution. We are not certain whether altered protein binding of the drug played a role in our patients, because we did not measure free drug concentration. Our patients showed a normal mean concentration of albumin. Inflammation in the intestine, liver, and spleen during typhoid fever (3) produces enlargement of these organs

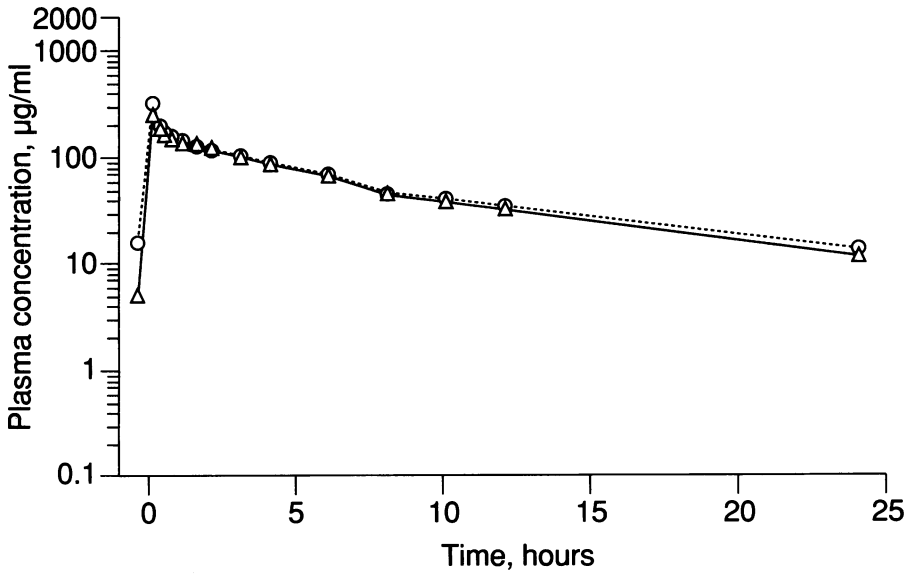

FIG. 1. Median plasma concentration-time profiles of ceftriaxone on day 1 (△) and day 3 (○) during and after intravenous infusion (30 min) of 3 g of ceftriaxone daily for 3 consecutive days.

and resultant accumulation of extravascular fluid into which an antibiotic can permeate. Distribution of ceftriaxone into inflamed spaces likely also contributed to its increase in volume of distribution.

Our patients were ethnic Nepalese, whereas values for healthy volunteers were from European subjects. Ethnic differences are primarily under genetic control, although environmental factors such as diet may also play a part. Genetically controlled interethnic differences mainly affect elimination by metabolism (22). Since ceftriaxone is not metabolized in humans (17), such an effect could be ruled out. Interethnic differences in distribution are also possible, but they are not very conclusive for ceftriaxone. Differences between Chinese and Caucasians in body fat were reported to be the most important interethnic variable influencing the volume of distribution of diazepam (10). Since ceftriaxone has a low lipid solubility and the volume of distribution corresponds to the aqueous extracellular space, interethnic differences in body lipid stores are assumed to have little effect on the volume of distribution of ceftriaxone. Since serum albumin concentrations in our study are within the normal range of Caucasians, interethnic differences in plasma protein binding are unlikely. Accordingly, we anticipate no clinically important interethnic pharmacokinetic differences for ceftriaxone. However, further studies of healthy subjects of different races will be required to exclude interethnic differences in pharmacokinetics.

The increased CL_R of ceftriaxone documented in this study is consistent with normal renal function in these patients with typhoid fever, who showed normal values of creatinine in serum and blood urea nitrogen. Although the mean of creatinine CLs was lower than normal, the short stature and low body weights of our patients, with resultant diminution in body surface area, caused the abnormality in creatinine CL to be mild. The increased total CL of ceftriaxone shown for these patients may have resulted, in part, from enhanced hepatic excretion into bile. In normal volunteers, ceftriaxone concentrations in bile and urine were similar (21), and the amount of a dose recovered in bile was 11 to 65% (2). Patients with typhoid fever often show hepatomegaly (3), and the patients in this study showed mild elevations of aspartate aminotransferase in serum, suggesting only modest injury to hepatocytes. Although we did not measure biliary excretion in this study, it is likely that ample excretion occurred by this route, because the normal values of serum bilirubin and gamma-glutamyltransferase indicated that hepatic excretory function was intact in these patients.

ACKNOWLEDGMENTS

We thank the nursing staff of the medical wards of the Teaching Hospital for their assistance. W. Ruch gave technical advice.

The work was supported by a grant from F. Hoffmann-La Roche Ltd. M. Ho was supported by the Alberta Heritage Foundation.

REFERENCES

1. **Anton, P. A., J. A. Kemp, T. Butler, and M. R. Jacobs.** 1982. Comparative efficacies of ceftriaxone, moxalactam and ampicillin in experimental *Salmonella typhimurium* infection. Antimicrob. Agents Chemother. **22**:312–315.
2. **Arvidsson, A., G. Alvan, B. Angelin, O. Borga, and C. E. Nord.** 1982. Ceftriaxone: renal and biliary excretion and effect on the colon microflora. J. Antimicrob. Chemother. **10**:207–215.
3. **Butler, T.** 1988. Typhoid fever, p. 1690–1691. *In* J. B. Wyngaarden, L. H. Smith, Jr., and J. C. Bennett (ed.), Cecil textbook of medicine, 19th ed. W. B. Saunders Co., Philadelphia.
4. **Chi-kin, L., C. Deh-lin, and R. Lasserre.** 1986. Two to three days treatment of typhoid fever with ceftriaxone. Southeast Asian J. Trop. Med. Public Health **17**:119–124.
5. **Coovadia, Y. M., V. Gathiram, A. Bhamjee, R. M. Garratt, K. Mlisana, N. Pillay, T. Madlalose, and M. Short.** 1992. An outbreak of multi-resistant *Salmonella typhi* in South Africa. Q. J. Med. New Ser. **82.298**:91–100.
6. **Edelman, R., and M. M. Levine.** 1986. Summary of an international workshop on typhoid fever. Rev. Infect. Dis. **8**:329–349.
7. **Findlay, C. D., R. M. Brown, J. E. Allcock, P. A. Lowe, and R. Wise.** 1982. A study of the relationship between dose and pharmacokinetics of ceftriaxone. J. Antimicrob. Chemother. **9**:57–62.
8. **Islam, A., T. Butler, S. K. Nath, N. H. Alam, K. Stoeckel, H. B. Houser, and A. L. Smith.** 1988. Randomized treatment of patients with typhoid fever by using ceftriaxone or chloramphenicol. J. Infect. Dis. **158**:742–747.
9. **Kalager, T., A. Digranes, T. Bergan, and C. O. Solberg.** 1984. The pharmacokinetics of ceftriaxone in serum, skin blister and thread fluid. J. Antimicrob. Chemother. **13**:479–485.
10. **Kumana, C. R., I. J. Lauder, M. Chan, W. Ko, and H. J. Lin.** 1987. Differences in diazepam pharmacokinetics in Chinese and white Caucasians—relation to body lipid stores. Eur. J. Clin. Pharmacol. **32**:211–215.
11. **Lasserre, R., R. P. Sangalang, and L. Santiago.** 1991. Three-day treatment of typhoid fever with two different doses of ceftriaxone, compared to 14-day therapy with chloramphenicol: a randomized trial. J. Antimicrob. Chemother. **28**:765–772.
12. **Mackowiak, P. A.** 1989. Influence of fever on pharmacokinetics. Rev. Infect. Dis. **11**:804–807.
13. **McNamara, P. J., K. Stoeckel, and W. H. Ziegler.** 1982. Pharmacokinetics of ceftriaxone following intravenous administration of a 3 g dose. Eur. J. Clin. Pharmacol. **22**:71–75.
14. **Naqvi, S. H., Z. A. Bhutta, and B. J. Farooqui.** 1992. Therapy of multidrug resistant typhoid in 58 children. Scand. J. Infect. Dis. **24**:175–179.
15. **Neu, H. C., N. J. Meropol, and K. P. Fu.** 1981. Antibacterial activity of ceftriaxone (Ro 13-9904), a β-lactamase-stable cephalosporin. Antimicrob. Agents Chemother. **19**:414–423.
16. **Stoeckel, K.** 1981. Pharmacokinetics of rocephin, a highly active new cephalosporin with an exceptionally long biological half-life. Chemotherapy (Basel) **27 (Suppl. 1)**:42–46.
17. **Stoeckel, K.** 1985. Selected aspects of ceftriaxone kinetics. *In* Development and treatment of infectious disease. Symposium Proceedings. Excerpta Medica, Amsterdam.
18. **Stoeckel, K., P. J. McNamara, R. Brandt, H. Plozza-Nottebrock, and W. H. Ziegler.** 1981. Effects of concentration-dependent plasma protein binding on ceftriaxone kinetics. Clin. Pharmacol. Ther. **29**:650–657.
19. **Svein, O.** 1986. Drug distribution and binding. J. Clin. Pharmacol. **26**:583–586.
20. **Ti, T. Y., E. H. Monteiro, S. Lam, and H. S. Lee.** 1985. Ceftriaxone therapy in bacteremic typhoid fever. Antimicrob. Agents Chemother. **28**:540–543.
21. **Trautmann, K. H., and P. Haelfelfinger.** 1981. Determination of the cephalosporin RO 13-9904 in plasma, urine, and bile by means of ion-pair reversed phase chromatography. J. High Resolut. Chromatogr. Chromatogr. Commun. **4**:54–59.
22. **Vesell, E. S.** 1980. Why are toxic reactions to drugs so often undetected initially? N. Engl. J. Med. **302**:1027–1029.