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Crossover Study of the Pharmacokinetics of Ceftriaxone Administered Intravenously or Intramuscularly to Healthy Volunteers

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The pharmacokinetics of ceftriaxone were investigated in six healthy adults. One-gram doses were administered either intramuscularly or intravenously in a crossover design study. Mean peak ceftriaxone concentrations in plasma of 79.2 and 123.2 μg/ml were achieved with intramuscular injection and intravenous infusion, respectively, with plasma half-lives of 5.4 and 5.8 h. The urinary recovery of ceftriaxone in the first 24 h was 37% after intravenous infusion and 25% after intramuscular injection.

The pharmacokinetic behavior of ceftriaxone was investigated in healthy volunteers to whom 1-g doses were administered intravenously (i.v.) and intramuscularly (i.m.) in a crossover study.

Six healthy adults, four males and two females (average age, 40.3 ± 14.6 years; average body surface area, 1.9 ± 0.2 m^2), were studied. All subjects gave written informed consent. The prestudy physical exam, hemogram, prothrombin time, and urinalysis were normal for each subject. Ceftriaxone was reconstituted in normal saline and 5% glucose for i.v. solutions and in 1% lidocaine for i.m. injection. Each subject received 1-g doses of ceftriaxone i.v., given as a 30-min infusion of 50 ml, and 10 ml i.m. at 1-week intervals, following a random crossover design. Subjects fasted overnight before drug administration and for 2 h thereafter and were sedentary during the study. Blood specimens were drawn from heparin locks inserted into the arm (contralateral during i.v. infusion) at 15, 30 (end of infusion), 40, 50, 60, and 90 min, at hourly intervals for another 10 h, and at 24 h after i.v. or i.m. doses. The blood was collected into preheparinized tubes, and plasma, separated by centrifugation, was stored at −65°C until analyzed.

Urine was collected before dosage and at 0 to 2, 2 to 4, 4 to 8, and 8 to 24 h. Volumes were recorded, and samples were filtered and stored at −65°C until assayed. Each plasma sample was deproteinized by adding 2.0 ml of acetonitrile and 0.75 ml of water to 0.25 ml of the sample in a test tube, followed by stirring for 15 s and centrifuging at 1,000 × *g* for 6 min. Plasma standards and samples were treated the same way. Concentrations of ceftriaxone in the supernatant were determined by an agar well diffusion method carried out in large plates (16 by 13 by 0.75 in.; Mast Labs, England) with *Escherichia coli* 1346 as the indicator organism and sterile distilled water as the diluent. Each plate contains its own set of standards, and a standard response curve was plotted for each plate (Bioassay of Ro 13-9904 in human plasma. Draft Standard Operation Procedures, Hoffmann-La Roche, Inc., Nutley, N.J., 1981).

The i.m. and i.v. data were analyzed by using one- and two-compartment pharmacokinetic models, respectively, by means of a program written for the Wang 700B advanced programmable calculator (10). The following parameters were calculated: elimination constant (K_e) ($hour^{-1}$); transfer rate constants between the central and peripheral compartments (K_{21} and K_{12}, respectively) ($hour^{-1}$); area under the curve (microgram · hour per milliliter); total apparent volume of distribution (V_d) (liters per kilogram); volume in the steady state (V_{dss}) (liters per kilogram); plasma clearance (liters per hour/1.73 m^2); renal clearance (liters per hour); and half-lives of the alpha distribution and beta elimination phases ($t_{1/2}\alpha$ and $t_{1/2}\beta$, respectively) (hours). The Loo and Riegelman (7) correction for the time of the i.v. infusion was applied to the data.

After 1-g i.m. doses, the mean level of ceftriaxone in plasma, obtained at 15 min, was 28.9 μg/ml; the mean levels in plasma at 2 and 24 h were 83.2 and 7.8 μg/ml, respectively (Table 1). The total quantity of ceftriaxone excreted between 4 and 8 h was 98 mg; 25% of the administered dose was excreted in the urine in the first 24-h period (Table 2).

TABLE 1. Concentrations (mean ± standard deviation) of ceftriaxone in plasma after 1-g doses administered either i.m. or i.v. in a crossover study

Time after dosage (h)	Route of administration	
	i.m.	i.v.
0	0	0
0.25	28.9 ± 26.4	79.7 ± 56.9
0.50	43.7 ± 34.5	123.2 ± 42.1[a]
0.66	35.2 ± 18.2	80.8 ± 41.3
0.83	51.2 ± 27.7	91.0 ± 44.1
1	62.3 ± 30.2	109.5 ± 56.7
1.5	79.2 ± 69.9	94.8 ± 43.3
2	83.2 ± 59.9	60.8 ± 26.2
3	95.2 ± 53.0	59.0 ± 27.7
4	58.5 ± 33.9	57.8 ± 26.9
6	40.6 ± 20.6	33.0 ± 17.4
8	41.3 ± 18.9	37.6 ± 24.6
12	35.5 ± 20.7	20.2 ± 15.3
24	7.8 ± 6.5	4.6 ± 1.9

[a] End of infusion.

After 1-g i.v. doses, the mean concentration of ceftriaxone in plasma was 79.7 μg/ml at 15 min ($P < 0.4$ when compared with i.m. doses by the Student t test), declining to 4.6 μg/ml by 24 h (Table 1); 37% of the administered dose was excreted in the urine during the 24-h period (Table 2).

After i.v. administration, the $t_{1/2}\beta$ was 5.8 h, the V_d was 0.2 liter/kg, the area under the curve was 830 μg · h/ml ($P = 0.2$ when compared with i.m. administration), and the plasma clearance was 1.2 liters per h/1.73 m^2. After i.m. administration, the terminal half-life was 5.4 h, the V_d was 0.19 liters/kg, the area under the curve was 903.5 μg · h/ml, and the plasma clearance was 1.5 liters per h/1.73 m^2 (Table 3).

The drug was well tolerated after either i.m. or i.v. administration.

The concentrations in plasma and urine after i.v. infusion observed in our study generally agree with those reported by Patel et al. (11). Volunteers given 1 g i.v. in our study excreted 37% of the administered dose in the urine in 24 h, whereas 44% was reported by Patel et al. (12) and 50% by Seddon et al. after 0.5-g doses (14). Similarly, after i.m. injection of 1 g in our study, 25% of the dose was excreted in 24 h, whereas Patel et al. (13) found that 34% was excreted after 0.5-g doses. There are extrarenal mechanisms for the elimination of ceftriaxone. Arvidsson et al. (2) reported that 11% of the dose was excreted unchanged in the bile.

Pharmacokinetic parameters derived in this study agree with previously published data. The $t_{1/2}\beta$ of 5.8 h after i.v. administration that we obtained is comparable with that of 6.2 h reported by Patel et al. (11), and there is similar agreement in the values of the area under the curve and V_d. In another report by Patel and colleagues (13) in which only i.m. injection of 0.5-g doses of ceftriaxone was studied, the $t_{1/2}$ was 7.1 h compared with the $t_{1/2}\beta$ of 5.4 h obtained in our study; the V_d was 9.37 liters compared with 0.2 liters/kg in our study. It should be noted, however, that values of dose-related increases in the V_d have previously been reported to be as high as 28% (16).

The concentrations of ceftriaxone attained in plasma, 4.6 and 7.8 μg/ml, 24 h after i.v. and i.m. doses, respectively, are significantly higher than the 90% minimal inhibitory concentration of drug for many gram-positive and gram-negative isolates (1, 15, 17); the mean concentrations in plasma 8 h after either route of administration (Table 1) would inhibit most strains of *Pseudomonas* and *Acinetobacter*. Even at 24 h, the mean urine concentrations of 210 and 360 μg/ml, after 1-g i.m. and i.v. doses, respectively, far exceed the 90% minimal inhibitory concentration of drug for most isolates encountered in clinical practice. These findings suggest that one dose daily will be adequate to treat even difficult urinary pathogens such as species of *Pseudomonas* and *Acinetobacter*. New cephalosporins such as moxalactam ($t_{1/2}\beta$, 2 h [8]), cefotaxime ($t_{1/2}\beta$, 1 h [6]), and cefoperazone ($t_{1/2}\beta$, 2 h [4]), and the new penicillins piperacillin, mezlocillin, and azlocillin ($t_{1/2}\beta$, 2 h [3, 5, 9]) require at least 3 to 6 doses daily for the treatment of seriously ill patients. Based on a $t_{1/2}\beta$ of 5.4 to 5.8 h, and high, sustained levels in plasma, ceftriaxone administered once daily should be effective against most infections. Controlled trials will be necessary to establish the clinical efficacy of such therapeutic regimens.

TABLE 2. Urinary excretion (mean ± standard deviation) or ceftriaxone after 1-g doses administered either i.m. or i.v.

h of urine collection	μg of ceftriaxone/ml of urine		mg in urine collection		% Dose excreted	
	i.m.	i.v.	i.m.	i.v.	i.m.	i.v.
0–2	294.2 ± 269.7	136.7 ± 213.2	32.8 ± 29.3	28.6 ± 46.97	3.3	2.8
2–4	246.7 ± 387.5	775.0 ± 80.8	24.6 ± 32.2	108.6 ± 106.7	2.5	10.9
4–8	625.0 ± 872.6	126.7 ± 210.4	65.1 ± 69.8	23.6 ± 42.5	6.5	2.4
8–24	210.0 ± 96.7	360.0 ± 318.9	127.7 ± 50.6	210.2 ± 120.4	12.8	21.0
0–24			250.2 ± 133.3	370.3 ± 159.96	25	37

TABLE 3. Pharmacokinetic parameters (mean ± standard deviation) of ceftriaxone after 1-g doses administered either i.m. or i.v. in a crossover study

Parameter[a]	Route of administration	
	i.m.	i.v.
Wt (kg)	72.3 ± 10.0	72.3 ± 10.0
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2
$t_{1/2}\alpha$ (h)		1.9 ± 0.8
$t_{1/2}\beta$ (h)	5.4 ± 0.8	5.8 ± 1.2
K_e (h^{-1})	0.1307 ± 0.2186	0.1812 ± 0.5428
K_{21} (h^{-1})		0.2686 ± 0.1027
K_{12} (h^{-1})		0.1183 ± 0.0724
V_1 (liters)		7.7 ± 3.0
V_d (liters/kg)	0.19 ± 0.15	0.2 ± 0.03
V_{dss} (liters/kg)		0.1 ± 0.02
AUC (μg · h/ml)	903.5 ± 588.9	830.0 ± 284.0
Plasma clearance (liters per h/1.73 m^2)	1.5 ± 1.1	1.2 ± 0.3
Renal clearance (liters/h)	0.4 ± 0.4	0.5 ± 0.2

[a] Abbreviations: BSA, bovine serum albumin; $t_{1/2}\alpha$, half-life of the alpha distribution phase; $t_{1/2}\beta$, half-life of the beta elimination phase; K_e, elimination constant; K_{21} (h^{-1}) and K_{12} (h^{-1}), transfer rate constants between the central and peripheral compartments, respectively; V_1, volume of the central compartment; V_{dss}, volume in the steady state; AUC, area under the curve.

LITERATURE CITED

1. **Angehrn, P., P. J. Probst, R. Reiner, and R. L. Then.** 1980. Ro 13-9904, a long-acting, broad-spectrum cephalosporin: in vitro and in vivo studies. Antimicrob. Agents Chemother. **18**:913–921.
2. **Arvidsson, A., G. Alan, 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. **Bergan, T.** 1978. Pharmacokinetics of mezlocillin in healthy volunteers. Antimicrob. Agents Chemother. **14**:801–806.
4. **Bolton, W. K., W. M. Scheld, D. A. Spyker, and M. A. Sande.** 1981. Pharmacokinetics of cefoperazone in normal volunteers and subjects with renal insufficiency. Antimicrob. Agents Chemother. **19**:821–825.
5. **Fiegel, P., and K. Becker.** 1978. Pharmacokinetics of azlocillin in persons with normal and impaired renal functions. Antimicrob. Agents Chemother. **14**:288–291.
6. **Fu, K. P., P. Aswapokee, I. Ho, C. Matthijssen, and H. C. Neu.** 1979. Pharmacokinetics of cefotaxime. Antimicrob. Agents Chemother. **16**:592–597.
7. **Loo, J. C. K., and S. Riegelman.** 1970. Assessments of pharmacokinetic constants from post infusion blood curves obtained after IV infusion. J. Pharm. Sci. **59**:53–55.
8. **Meyers, B. R., S. Z. Hirschman, J. Giron, and E. S. Srulevitch.** 1982. Pharmacokinetic studies of single and multiple doses of moxalactam (Moxam) in normal volunteers. Clin. Trials J. **19**:63–73.
9. **Meyers, B. R., S. Z. Hirschman, L. Strougo, and E. Srulevitch.** 1980. Comparative study of piperacillin, ticarcillin, and carbenicillin pharmacokinetics. Antimicrob. Agents Chemother. **17**:608–611.
10. **Meyers, B. R., S. Z. Hirschman, S. Yancovitz, and B. Ribner.** 1976. Pharmacokinetic parameters of sisomicin. Antimicrob. Agents Chemother. **10**:25–27.
11. **Patel, I. H., S. Chen, M. Parsonnet, M. R. Hackman, M. A. Brooks, J. Konikoff, and S. A. Kaplan.** 1981. Pharmacokinetics of ceftriaxone in humans. Antimicrob. Agents Chemother. **20**:634–641.
12. **Patel, I. H., K. Miller, R. Weinfeld, and J. Spicehandler.** 1981. Multiple intravenous dose pharmacokinetics of ceftriaxone in man. Chemotherapy (Basel) **27**(Suppl. 1):47–56.
13. **Patel, I. H., R. E. Weinfeld, J. Konikoff, and M. Parsonnet.** 1982. Pharmacokinetics and tolerance of ceftriaxone in humans after single-dose intramuscular administration in water and lidocaine diluents. Antimicrob. Agents Chemother. **21**:957–962.
14. **Seddon, M., R. Wise, A. P. Gillett, and R. Livingston.** 1980. Pharmacokinetics of Ro 13-9904, a broad-spectrum cephalosporin. Antimicrob. Agents Chemother. **18**:240–242.
15. **Shannon, K., A. King, C. Warren, and I. Phillips.** 1980. In vitro antibacterial activity and susceptibility of the cephalosporin Ro 13-9904 to beta-lactamases. Antimicrob. Agents Chemother. **18**:292–298.
16. **Stoeckel, K. P., J. McNamara, R. Brandt, H. Plozza-Nottebrock, and W. H. Ziegler.** 1981. The effects of concentration-dependent plasma-protein binding on ceftriaxone kinetics. Clin. Pharmacol. Ther. **29**:650–657.
17. **Wise, R. A., A. P. Gillett, J. M. Andrews, and K. A. Bedford.** 1980. Ro 13-9904, a new cephalosporin with a high degree of activity and antibacterial activity: an *in vitro* comparative study. J. Antimicrob. Chemother. **6**:595–600.