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Intramuscular and Intravenous Pharmacokinetics of Cefmenoxime, a New Broad-Spectrum Cephalosporin, in Healthy Subjects

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This study was concerned with the single-dose, pharmacokinetics of cefmenoxime after intramuscular (i.m.) injections of 250, 500 and 1,000 mg; 1-h intravenous (i.v.) infusions of 500, 1,000, and 2,000 mg; and 5-min i.v. injections of 500, 1,000, and 2,000 mg of cefmenoxime. A total of 15 subjects were used, each receiving all three doses for one route of administration. Mean calculated peak plasma levels after the 250-, 500-, and 1,000-mg i.m. doses were 9.07, 14.68, and 26.73 μg/ml, respectively, occurring about 40 min after dosing. The biphasic decline in plasma levels after i.v. administration was usually not apparent after i.m. dosing, because absorption of the drug from the injection depot was slower than distribution of the drug. Mean calculated peak levels from the 500-, 1,000-, and 2,000-mg i.v. doses were 22.8, 41.6, and 94.5 μg/ml, respectively, after the 1-h infusions and 64.1, 100.9, and 198.2 μg/ml, respectively after the 5-min injections. Small but statistically significant trends of decreasing alpha and increasing volume of distribution (central compartment) with increasing dose size were noted; however, this distribution phenomenon was self-compensating, resulting in no overall effect on plasma clearance. For practical purposes, the pharmacokinetics were linear. The mean 0- to 24-h urinary recoveries of cefmenoxime after the i.m. injections, i.v. infusions, and i.v. injections were 72.1, 67.5, and 74.5% respectively. Overall, the pharmacokinetics of cefmenoxime were best described by a two-compartment open model with a beta-phase half-life of 0.91 h. Plasma clearance of the drug was dosage level and route independent, averaging 254 ml/min; thus, there was an excellent linear relationship between the area under the plasma level curve and the dose. The results of this study indicated that most of the drug is removed by renal mechanisms, with tubular secretion predominating.

This study is concerned with the pharmacokinetics of cefmenoxime, a new broad-spectrum semisynthetic cephalosporin (4, 7, 8) after intramuscular (i.m.) injections of 250, 500, and 1,000 mg; 1-h intravenous (i.v.) infusions of 500, 1,000, and 2,000 mg; and 5-min i.v. injections of 500, 1,000, and 2,000 mg.

MATERIALS AND METHODS

Volunteers. Fifteen healthy adult male volunteers participated in this study after giving informed consent. A complete physical examination, a chest X-ray, an ophthalmological examination, and a panel of laboratory tests including a complete hematology, clinical chemistries, a urinalysis, and a direct Coombs' test were performed on each subject before and after the study. Ages of the subjects ranged from 20 to 35 years, heights ranged from 163 to 183 cm, and weights ranged from 60.8 to 81.6 kg.

Study design. The 15 subjects were randomly apportioned into three groups of 5 subjects. Subjects 1 through 5 each received single 250-, 500-, and 1,000-mg doses of cefmenoxime as bolus i.m. injections at 3-day intervals. Similarly, subjects 6 through 10 and 11 through 15 each received 500, 1,000, and 2,000-mg doses of cefmenoxime by 1-h i.v. infusion and by 5-min i.v. injections, respectively, all with an infusion pump (Lifecare System, Abbott Laboratories, North Chicago, Ill.), at each collection.

Approximately 10 ml of heparinized venous blood were collected at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h after initiation of the i.m. and i.v. injections; and at 0, 0.25, 0.5, 1, 1.33, 1.67, 2, 3, 4, 6, 8, and 12 h after initiation of the 1-h i.v. infusion. These samples were promptly centrifuged, and the resultant plasmas were stored frozen until analyzed. Samples (10 ml) from a predosing collection and from the complete urine collections at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdosing were also saved for analysis.

Analytical methods. Urine samples were analyzed microbiologically with *Proteus mirabilis* (strain 13300, Takeda Chemical Industries, Ltd., Osaka, Japan) as the test organism, with a limit of quantification of about 5.0 μg/ml. Plasma samples were assayed by a precise high performance liquid chromatographic pro-

cedure developed in our laboratory, with a limit of quantification of about 0.05 μg/ml. Basically, the procedure consisted of displacing the cefmenoxime from plasma proteins with sodium dodecyl sulfate and then deproteinizing the plasmas by ultrafiltration, followed by injection onto a Micro-Bondapak C_{18} high-performance liquid chromatographic column, with an eluent of 13% acetonitrile in 0.2 *F* acetate buffer adjusted to pH 5.30. The eluent was monitored for UV absorption at a wavelength of 254 nm. The coefficient of variation of this assay was slightly greater than 1%.

Pharmacokinetic analysis. The pharmacokinetic fits of plasma time-concentration data were obtained by using NONLIN (3), with reciprocal squared concentrations as weights for the individual subjects and with reciprocal intersubject concentration variances as weights for the mean data (1).

Data from the i.v. dosings were subjected to sequential polyexponential regression analysis by using STRIP, which is a slightly modified version of CSTRIP (6). Based on the criteria of Sedman and Wagner (5), the bioexponential model (*i.e.*, a two-compartment open pharmacokinetic model) was selected to best describe the data. Fittings were performed by using a DFUNC subroutine, written by the authors and programmed with two-compartment model infusion equations (elimination from central compartment), with microscopic rate constants (K_{21}, K_{12}, K_{Nel}, and V_1) as the estimated parameters. Equations used were those of Gibaldi and Perrier (2). Although subjects in this study were actually dosed with the hemihydrochloride salt form of cefmenoxime, drug concentrations and dose sizes are stated throughout this report in terms of cefmenoxime free base.

RESULTS AND DISCUSSION

The results of the plasma level determinations from the 1-h i.v. infusions, 5-min i.v. injections, and the bolus i.m. injections are shown in Figure 1. The corresponding mean urinary excretion data from the three dose routes are presented in Table 1.

i.v. infusion. The NONLIN results for the 1-h i.v. infusion data are presented in Table 2. The mean data for this group are plotted in Fig. 1, with the best-fit lines thereto.

Mean observed peak levels of cefmenoxime at the terminations of the 500-, 1,000-, and 2,000-mg infusions were 22.7, 41.7, and 89.7 μg/ml, respectively. The corresponding mean NONLIN-calculated peak levels were 22.8, 41.6, and 94.5 μg/ml. The postinfusion decline in the levels was biphasic, with a mean beta-phase half-life of 0.86 h.

The plasma clearance for this group averaged 275 ml/min and showed no dose-related trends. Mean urinary recoveries of cefmenoxime after the 500-, 1,000-, and 2,000-mg infusions were 77.6, 63.9, and 48.6%, respectively. Isolated cases of what might have been incomplete urine collections were noted, but were not great enough to appreciably alter the results. The overall urinary recovery for the infusion portion

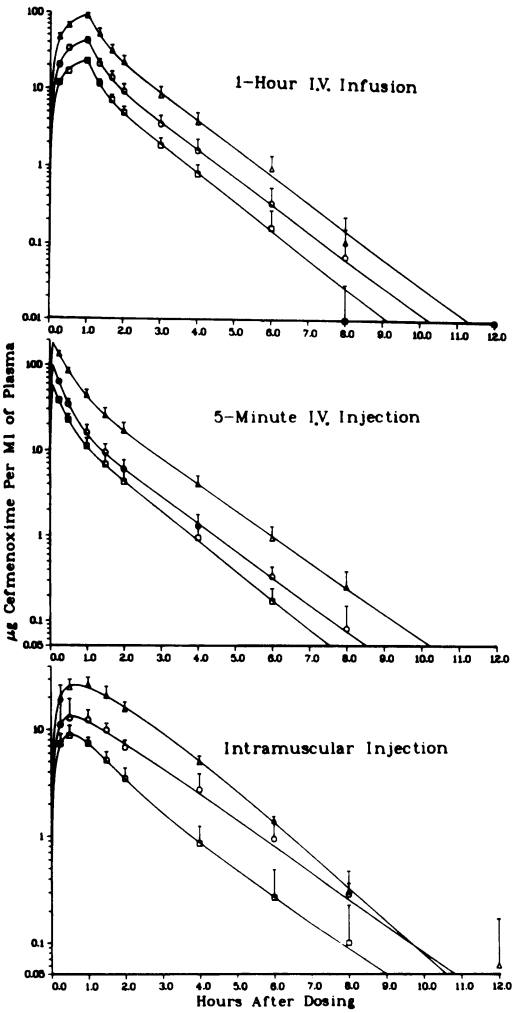

FIG. 1. Mean plasma levels (+SD) of cefmenoxime from various dosings.

of the study was 67.5%. Based on this figure and on the mean plasma clearance, an uncorrected renal clearance of 186 ml/min could be calculated. When corrections for plasma protein binding were taken into account, it became evident that the predominant elimination route was renal tubular secretion.

i.v. injection. The results of the NONLIN pharmacokinetic analyses of the i.v. injection data are given in Table 2. Mean data + standard deviation (SD) and corresponding best-fit lines are plotted in Fig. 1.

The mean calculated peak levels of cefmenoxime after the 500, 1,000, and 2,000-mg 5-min, zero-order injections were 64.1, 100.9, and 198.1 μg/ml, respectively. Plasma levels declined in a distinctly biphasic fashion, falling to one-fifth of peak values in h 1. The average beta-phase half-life was 0.91 h. No major dose-related trends

TABLE 1. Mean urinary excretion data for cefmenoxime

Injection or infusion (mg)	Interval (h) after dose	Vol (ml)	Concn (μg/ml)	Amt excreted (mg)
500 (i.v.)	0–4	338	1,167.08	373.58
	4–8	184	91.74	17.61
	8–12	278	7.57	1.17
	12–24	904	0.00	0.00
1,000 (i.v.)	0–4	275	1,949.24	550.90
	4–8	184	271.68	51.47
	8–12	282	12.13	3.26
	12–24	770	0.00	0.00
2,000 (i.v.)	0–4	226	5,851.32	1,267.45
	4–8	262	602.68	129.29
	8–12	346	32.03	9.63
	12–24	726	1.06	0.78
500 (i.v.)[a]	0–4	570	673.69	370.74
	4–8	322	53.96	17.25
	8–12	385	0.00	0.00
	12–24	906	0.00	0.00
1,000 (i.v.)[a]	0–4	360	1,741.63	599.20
	4–8	115	304.63	36.98
	8–12	376	7.27	2.59
	12–24	719	0.00	0.00
2,000 (i.v.)[a]	0–4	249	3,621.07	850.80
	4–8	353	167.33	49.75
	8–12	402	125.63	50.72
	12–24	776	88.79	19.95
250 (i.m.)	0–4	154	1,095.98	154.23
	4–8	235	163.59	32.42
	8–12	307	9.84	1.66
	12–24	641	0.00	0.00
500 (i.m.)	0–4	172	1,668.56	262.79
	4–8	228	359.54	81.11
	8–12	380	52.05	19.97
	12–24	909	0.00	0.00
1,000 (i.m.)	0–4	130	3,151.32	394.54
	4–8	267	693.62	178.26
	8–12	463	32.31	9.84
	12–24	835	0.00	0.00

[a] Infusion.

were observed in plasma clearance (*i.e.*, dose-normalized area under the curve); hence, as a first approximation, the pharmacokinetics appeared to be linear. Mean urinary recoveries of cefmenoxime after the 500-, 1,000-, and 2,000-mg i.v. injections were 78.5, 74.7, and 70.4%, respectively.

The mean plasma clearance of cefmenoxime for this group of subjects was 245 ml/min. Based on this figure and on a mean urinary recovery of 74.5%, the mean uncorrected renal clearance was 182 ml/min. Our earlier studies yielded plasma protein binding estimates of about 77%. Since the renal clearance corrected for plasma protein binding would have been several times higher than the glomerular filtration rate, tubular secretion of the drug in humans must have been the dominant process.

i.m. injection. The results of NONLIN pharmacokinetic analyses of the i.m. data with a two-compartment open model are given in Table 2. Fig. 1 comprises plots of the mean data (+SD) with the corresponding nonlinear regression lines.

Although the decline in the cefmenoxime plasma levels was distinctly biphasic after the i.v.

TABLE 2. Summary of NONLIN fits of plasma cefmenoxime level data

Injection or infusion (mg)		K_a (h^{-1})	Alpha (h^{-1})	$t_{1/2}$ beta (h)	K_{21} (h^{-1})	K_{12} (h^{-1})	K_{net} (h^{-1})	V_1 (liter)	0–Inf AUC[a] (μg./ml)	C_{max} (μg/ml)	t_{max} (h)
500 (i.v.)[b]	Means of fits			0.78	1.77	1.35	2.23	7.40	30.8	22.8	
	SD			0.10	0.41	0.57	0.36	0.60	3.6	2.0	
	Fit of means			0.82	1.58	1.12	2.16	7.43	31.1	23.1	
1,000 (i.v.)[b]	Means of fits			0.85	1.54	1.12	2.08	8.81	57.3	41.6	
	SD			0.26	0.55	0.53	0.48	1.83	7.4	3.5	
	Fit of means			0.86	1.43	0.89	1.96	8.82	57.7	42.4	
2,000 (i.v.)[b]	Means of fits			0.97	1.11	0.56	1.73	9.04	131.1	94.5	
	SD			0.12	0.15	0.17	0.29	1.06	18.1	9.6	
	Fit of means			0.85	1.53	0.93	1.86	8.29	129.4	92.9	
500 (i.v.)	Means of fits			0.85	1.81	1.30	1.86	7.20	39.3	64.1	
	SD			0.07	0.79	1.11	0.33	1.69	7.9	14.3	
	Fit of means			0.87	1.69	0.98	1.68	7.93	37.6	56.7	
1,000 (i.v.)	Means of fits			0.94	1.32	0.90	1.94	8.90	59.6	100.9	
	SD			0.08	0.14	0.14	0.41	0.91	7.4	8.7	
	Fit of means			0.95	1.34	0.97	1.89	9.05	58.5	98.4	
2,000 (i.v.)	Means of fits			0.95	1.49	0.81	1.53	9.28	143.3	198.2	
	SD			0.12	0.29	0.25	0.20	1.05	13.2	21.6	
	Fit of means			0.99	1.32	0.65	1.43	9.92	140.6	185.2	
250 (i.m.)	Means of fits	1.51	3.24	1.15	1.00	0.88	1.96	7.55	17.7	9.07	0.57
	SD	0.37	0.79	0.19	0.21	0.44	0.50	1.29	2.1	1.44	0.11
	Fit of means	1.51	2.95	1.24	0.94	0.81	1.77	7.95	17.8	8.97	0.55
500 (i.m.)	Means of fits	1.19	3.37	0.97	1.32	0.98	1.77	8.94	34.8	14.68	0.77
	SD	0.57	1.28	0.33	0.42	0.75	0.52	3.12	4.6	5.08	0.41
	Fit of means	0.97	4.63	1.19	1.14	1.70	2.37	6.16	34.2	13.40	0.57
1,000 (i.m.)	Means of fits	1.22	4.27	0.85	2.01	1.41	1.66	8.95	69.0	26.73	0.74
	SD	0.70	2.19	0.20	0.71	1.40	0.32	1.28	7.2	4.50	0.17
	Fit of means	0.85	4.35	0.86	1.54	1.34	2.28	6.27	69.8	26.40	0.67

[a] 0–inf AUC, Area under the zero to infinity plasma level curve.
[b] Infusion.

administration, this was not the case after i.m. injection. This phenomenon occurs in cases in which the rate constant for absorption from the i.m. injection site is smaller than either of the macroscopic distribution or elimination rate constants, alpha and beta. For the two-compartment model after i.m. administration, the conditions and equation for the classical case are:

$$K_a > \text{alpha} > \text{beta with } C_t = -Ce^{-K_a(t)} + Ae^{-\text{alpha}(t)} + Be^{-\text{beta}(t)}$$

In the present case though, the following situations exist:

$$\text{alpha} > K_a > \text{beta with } C_t = Ce^{-K_a(t)} - Ae^{-\text{alpha}(t)} + Be^{-\text{beta}(t)},$$

$$\text{or } C_t = -Ce^{-K_a(t)} - Ae^{-\text{alpha}(t)} - Be^{-\text{beta}(t)}$$

In all cases with cefmenoxime, the rate constant controlling the postinjection rise in plasma levels is the distribution phase rate constant alpha or a combination of alpha with beta or with K_a.

Obviously, NONLIN analysis of such data with a two-compartment model, when a distribution phase is not evident and alpha > K_a, would not be meaningful unless constraints were imposed on the parameters; hence, the mean parameters from the infusion fits ±2 SD were used as the initial estimates and their constraints. The rate constant for absorption of drug from the injection site was about 1.3 h^{-1} ($t_{1/2}$ = 0.53 h). The apparent plasma (terminal phase) half-life in the i.m. portion of the study was longer than those from the i.v. administrations because two exponential processes (K_a and beta) of similar magnitude were controlling the decline in the levels in the former case. In other words, the half-life was longer than the i.m. administration because the relatively slow absorption of drug was still occurring after levels had peaked and

had begun to decline. Indeed, in five cases, the slowest rate process was absorption (beta > K_a).

The mean urinary recoveries of cefmenoxime for the 250-, 500-, and 1,000-mg dose groups were 75.3, 72.8, and 58.3%, respectively. The overall mean recovery for all i.m. dosings was 72.1%. The mean plasma clearance was 242 ml/min; thus, the uncorrected renal clearance was about 172 ml/min.

Comparison of dosing routes. Plasma clearances of cefmenoxime were consistently in the same range for the different routes of administration and between dosage levels; thus, for practical purposes, the pharmacokinetics were linear. Relationships between both trapezoidal (0 to 12 h) and NONLIN-estimated (0 to infinity) area under the curve versus dose were highly linear (r = 0.987 and 0.989, respectively), with Y-intercepts that were not significantly different from zero.

Analysis of variance and linear regressions were conducted on the data of Table 2, seeking dose-related trends in the various parameters. Neither renal clearance nor beta appeared to be dose-dependent. Marginally significant trends were noted in the regressions of alpha versus dose and V_1 (volume of central compartment) versus dose.

$$\text{Alpha} = -0.00045(\pm 0.00018) \times \text{dose} + 3.86(\pm 0.28)$$

$$V_1 = 0.00111(\pm 0.00027) \times \text{dose} + 7.19(\pm 0.31)$$

The elimination of cefmenoxime comprises a first-order event (glomerular filtration) and two processes capable of demonstrating Michaelis-Menten kinetics (tubular secretion and biliary secretion); hence, the higher plasma levels associated with increasing dose size (particularly after i.v. injection or infusion) would be expected to shift the relative contribution of each process if one of the two saturable mechanisms begins to deviate from pseudo- first-order kinetics. For example, if this is the case with renal tubular secretion, the apparent distribution of the cephalosporin would change in a fashion similar to the trends noted above.

The decreases in K_{net} and in alpha with increasing dose size are accompanied by increases in V_1; thus, plasma clearance is unaffected, relegating the overall effect to a low order of practical significance. Accordingly, additional attempts to fit the data to a more complex model are unwarranted.

The mean intrasubject coefficients of variation in plasma clearance for the i.m. injections, i.v. infusions, and i.v. injections were approximately 3, 9, and 16%, respectively, averaging about 9% overall. The corresponding respective mean intersubject coefficients of variation were 12, 12, and 14%. In an attempt to locate the source of the intersubject variance, mean intrasubject creatinine clearances were calculated from data collected on study days −1, 1, 4, 7, and 8; these mean values were then compared with mean intrasubject plasma clearances and renal clearances of cefmenoxime. The slopes of the linear regression analyses were not statistically significant, primarily because the range in the creatinine clearances for these normal healthy adult males was fairly small. Reduced plasma and renal clearances would be expected, however, for subjects with various degrees of compromised renal function.

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LITERATURE CITED

1. **Boxenbaum, H. G., S. Riegelman, and R. M. Elashoff.** 1974. Statistical estimations in pharmacokinetics. J. Pharmacokin. Biopharm. 2:123–148.
2. **Gibaldi, N., and D. Perrier.** 1975. Pharmacokinetics. Marcel Dekker, Inc., New York.
3. **Metzler, C. M., G. L. Elfring, and A. J. McEwen.** 1974. A package of computer programs for pharmacokinetic modeling. Biometrics 30:562–563.
4. **Ochiai, M., O. Aki, A. Morimoto, T. Okada, and Y. Matsushita.** 1977. New cephalosporin derivatives with high antibacterial activities. Chem. Pharm. Bull. 25:3115–3117.
5. **Sedman, A. J., and J. G. Wagner.** 1974. AUTOAN—a decision-making computer program, p. 16 Publication Distribution Service, Ann Arbor, Michigan.
6. **Sedman, A. J., and J. G. Wagner.** 1976. CSTRIP, a FORTRAN IV computer program for obtaining initial polyexponential parameter estimates. J. Pharm. Sci. 65:1006–1010.
7. **Stamm, J. M., R. L. Girolami, N. L. Shipkowitz, and R. R. Bower.** 1981. Antimicrobial activity of cefmenoxime (SCE-1365). Antimicrob. Agents Chemother. 19:454–460.
8. **Tsuchiya, K., M. Kondo, M. Kida, M. Nakao, T. Iwahi, T. Nishi, Y. Noji, M. Takeuchi, and Y. Nozaki.** 1981. Cefmenoxime (SCE-1365), a novel broad-spectrum cephalosporin: *in vitro* and *in vivo* antibacterial activities. Antimicrob. Agents Chemother. 19:56–65.