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Cefoperazone Pharmacokinetics in Normal Subjects and Patients with Cirrhosis

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The pharmacokinetics of cefoperazone were studied and compared in six normal subjects and six patients with severe liver disease. All subjects received a 2-g intravenous infusion of cefoperazone over 15 min. Significantly different results were noted between normal subjects and patients with cirrhosis (range [mean]) for the following: peak serum concentrations (203 to 345 [239] versus 82 to 206 [141] μg/ml; $P < 0.01$); serum β half-lives (1.0 to 1.8 [1.5] versus 2.3 to 9.9 [4.5] h; $P < 0.05$); renal excretion (17 to 27 [21] versus 32 to 60 [50]%; $P < 0.01$); and apparent volumes of distribution at steady state (4.1 to 7.8 [6.3] versus 12.7 to 23.8 [15.9] liters/1.73 m^2; $P < 0.01$). Lower peak serum levels in the patients with cirrhosis were probably related to an increased apparent volume of distribution secondary to ascites and to decreased serum protein binding of cefoperazone. Longer β half-lives in the patients with cirrhosis were probably secondary to both decreased hepatic excretion caused by severe liver disease and to increased apparent volume of distribution. However, the longest β half-life among the patients with cirrhosis was in a subject with a serum creatinine level of 2.1 mg/dl. We conclude that, although mild to moderate impairment of cefoperazone excretion occurs in patients with hepatic disease, adjustment of dosage may be necessary only with concomitant renal insufficiency.

Cefoperazone is a new, semisynthetic cephalosporin which, unlike presently available cephalosporins, is eliminated primarily by hepatobiliary rather than renal excretion (R. Bundtzen, W. Craig, R. Toothaker, M. Brodey, A. Gerber, and P. Welling, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 112; M. B. Rosenfeld, K. R. Ratzan, and I. Lauredo, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 114). Excretion of this antibiotic is not significantly impaired in patients with renal insufficiency (1, 3); however, there have been several reports that excretion of cefoperazone is reduced in patients with hepatobiliary disease (4; L. A. Wheeler, N. Kaplowitz, and S. M. Finegold, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 755; W. A. Craig, R. Greenfield, M. Goetz, and B. Vogelman, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 756). The purpose of this study was to determine the effect of impaired hepatic function on the pharmacokinetics of cefoperazone. The results demonstrate only mild to moderate impairment of cefoperazone excretion in patients with hepatic disease unless concomitant renal dysfunction is also present.

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MATERIALS AND METHODS

The pharmacokinetics of cefoperazone were studied in six healthy volunteers and six patients with cirrhosis. Criteria for the inclusion of patients with cirrhosis were a history of chronic liver disease with a clinical or biopsy diagnosis of cirrhosis; splenomegaly; and a serum albumin concentration of <3.0 g/dl.

Laboratory tests performed on the subjects included prothrombin time and tests for levels of serum albumin, bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and creatinine.

Cefoperazone (2 g) in 50 ml of 5% glucose in water was infused intravenously (i.v.) over 15 min. Venous blood was collected at regular intervals, and the serum was separated. Serum and urine samples were stored at −20°C until time of assay.

Cefoperazone serum and urine levels were measured by high-pressure liquid chromatography (P. Hwang and M. C. Meyer, J. Liq. Chromatogr., in press). Assayable samples were produced by combining one part serum or urine, one part 100% methanol, and one part 100% methanol containing the internal

standard, hydrochlorothiazide. These mixtures were vortexed for 20 s, allowed to stand at room temperature for 10 min, and centrifuged at 1,400 × *g* for 10 min. Assayable supernatants were separated from the precipitates and kept on ice until analyzed. The chromatographic eluent was a mixture of 2.4 ml of 1 M triethylamine in acetonitrile, 5.6 ml of 1 M acetic acid, 240 ml of acetonitrile, and 752 ml of deionized water. Analysis was performed on a system composed of a model M-45 solvent delivery system, model M-U6K injector, and Radial-Pak μ-Bondapak C_{18} cartridge in a Z module (all from Waters Associates, Milford, Mass.). The samples were monitored by a model 480 LC spectrophotometer set at 254 nm, and results were collected on an M730 data module (both from Lambda-Max, Milford, Mass.). The within-day and between-day coefficients of variation for the assay were 3 to 4%.

The semilogarithmic plot of the serum concentrations of cefoperazone versus time after i.v. infusion conformed to a biexponential curve with an initial α (distribution) phase and a subsequent β (elimination) phase. The slopes of the α and β phases, along with the zero time intercepts (*A* and *B*) for the respective concentration curves, were determined by exponential curve fitting (9). The serum half-life for the β phase ($t_{1/2\beta}$) was defined as: $t_{1/2\beta}$ = (ln 2)/(slope of β). Pharmacokinetic parameters were calculated after correcting for the elimination of cefoperazone during the 15-min infusion by the formulas of Loo and Riegleman (8). The area under the serum concentration-time curve (AUC; in microgram · hours per milliliter) was calculated from the formula: AUC = $A/\alpha + B/\beta$ (7). The serum clearance (Cl_s; in milliliters per minute per 1.73 m^2) of cefoperazone was calculated from the formula (7):

$$Cl_s = \frac{\text{dose}}{\text{AUC} \times 60} \times \frac{1.73}{\text{BSA}}$$

where the dose is in micrograms and the body surface area (BSA) is in square meters, calculated from the DuBois formula (6) with the height and weight of each subject. The renal clearance (Cl_r; in milliliters per minute per 1.73 m^2) of cefoperazone was determined 0 to 8 h and 0 to 12 h after i.v. infusion of the drug in normal subjects and patients with cirrhosis, respectively, from the formula:

$$Cl_r = \frac{U_{t1\rightarrow t2}}{\text{AUC}_{t1\rightarrow t2} \times 60} \times \frac{1.73}{\text{BSA}}$$

where $U_{t1\rightarrow t2}$ is the cefoperazone concentration, in micrograms per milliliter, excreted in the urine during the time interval $t1\rightarrow t2$, and $\text{AUC}_{t1\rightarrow t2}$ is the AUC during the same time interval. Renal excretion was determined as the percent i.v. dose of cefoperazone appearing in the urine from 0 to 8 h in normal subjects and 0 to 12 h in patients with cirrhosis. The apparent volume of distribution at steady state (V_{dss}; in liters per 1.73 m^2) of cefoperazone was calculated from the formula (2):

$$V_{dss} = \frac{\text{dose} \times \text{AUMC}}{\text{AUC}^2 \times 1{,}000} \times \frac{1.73}{\text{BSA}}$$

where AUMC is the area under the first moment of the serum concentration-time curve in microgram · (hours) squared per milliliter.

Statistical analysis used to compare cefoperazone pharmacokinetic parameters between normal subjects

TABLE 1. Demographic characteristics, hepatic and renal function tests, and serum $t_{1/2\beta}$s for normal subjects and patients with cirrhosis[a]

Patients	Sex	Age (yr)	BSA (m^2)	Hepatic disease	Ascites	Prothrombin time (11–14 s)	Albumin (3.5–5.0 mg/dl)	Total bilirubin (0–1.1 mg/dl)	Alkaline phosphatase (30–85 U/liter)	SGOT (0–27 U/liter)	SGPT (0–27 U/liter)	Creatinine (0.8–1.4 mg/dl)	$t_{1/2\beta}$ (h)
Normal													
1	M	26	2.08	None	No	NA	4.3	0.4	93	17	18	1.2	1.8
2	M	31	2.13	None	No	NA	4.8	0.8	41	21	30	1.1	1.8
3	M	25	1.69	None	No	NA	4.4	0.6	55	15	10	0.9	1.5
4	F	28	1.50	None	No	NA	4.2	0.3	41	12	3	0.6	1.0
5	M	26	1.90	None	No	NA	4.7	0.6	63	21	16	1.0	1.5
6	M	28	1.76	None	No	NA	4.8	0.9	88	29	33	1.0	1.6
Cirrhotic													
1	F	55	1.69	AC	Yes	16	2.5	2.0	160	49	14	0.6	3.5
2	M	49	1.85	AC	Yes	14	2.8	3.4	103	13	2	2.1	9.9
3	M	29	1.94	BC	No	16	1.6	4.4	248	74	29	1.0	2.8
4	M	62	2.06	AC	Yes	14	2.7	0.9	142	28	14	1.2	5.0
5	F	51	1.48	AC	Yes	21	2.2	4.3	311	41	11	0.7	2.3
6	M	37	2.04	AC	Yes	26	2.4	12	246	122	27	0.9	3.5

[a] Normal laboratory values and units appear under each test. BSA, Body surface area; SGOT, serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase; AC, alcoholic cirrhosis; BC, secondary biliary cirrhosis; NA, not available.

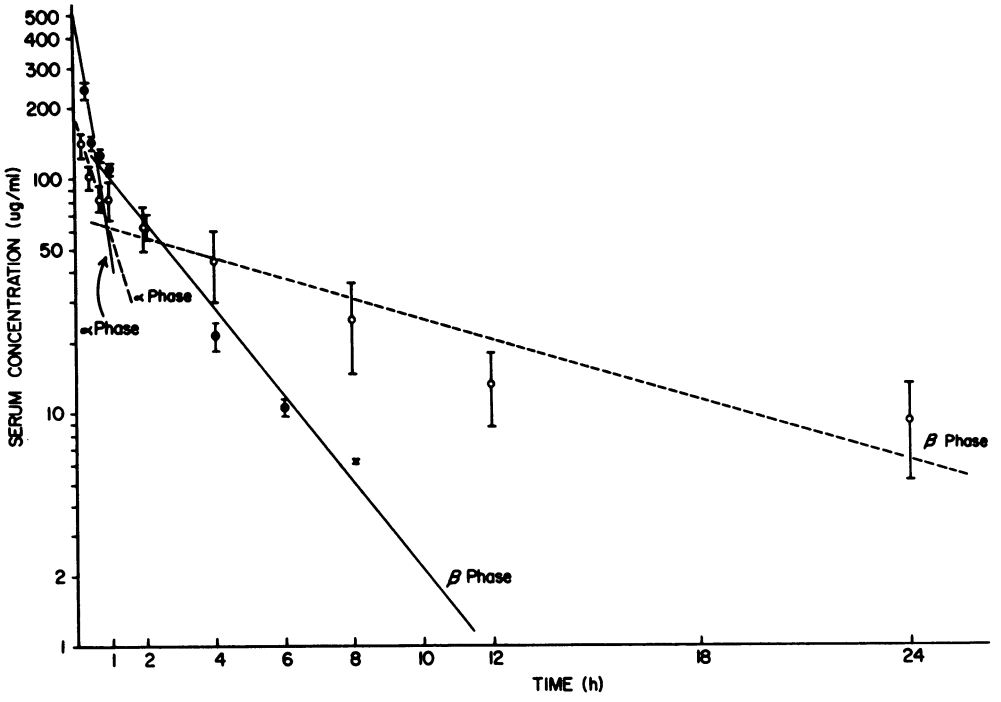

FIG. 1. Mean ± standard error serum concentrations of cefoperazone in six normal subjects (●) and six patients with cirrhosis (○) after a 2-g i.v. infusion given over 15 min.

and patients with cirrhosis were performed using Student's *t* test.

RESULTS

The demographic characteristics, hepatic and renal function tests, and serum $t_{1/2\beta}$s for normal subjects and patients with cirrhosis are listed in Table 1. The six patients with cirrhosis had severe liver disease: five had alcoholic cirrhosis with ascites and one had secondary biliary cirrhosis without ascites. Serum albumin levels were ≤2.8 mg/dl. Patient 2, who had cirrhosis, had an elevated serum creatinine level of 2.1 mg/dl.

The mean ± standard error serum concentrations of cefoperazone for normal subjects and patients with cirrhosis are shown in Fig. 1. The α-phase slopes were similar in both groups; however, the β-phase slopes of the patients with cirrhosis were less steep than those of the normal subjects.

The cefoperazone pharmacokinetics (peak serum concentration immediately after the end of infusion, serum $t_{1/2\beta}$, Cl_s, Cl_r, renal excretion, and V_{dss} for normal subjects and patients with cirrhosis are presented in Table 2. Statistically significant differences were noted between normal subjects and patients with cirrhosis (range [mean]) for: peak serum concentrations (203 to 345 [239] versus 82 to 206 [141] μg/ml; $P < 0.01$); serum $t_{1/2\beta}$s (1.0 to 1.8 [1.5] versus 2.3 to 9.9 [4.5] h; $P < 0.05$); renal excretion (17 to 27 [21] versus 32 to 60 [50]%; $P < 0.01$); and V_{dss} (4.1 to 7.8 [6.3] versus 12.7 to 23.8 [15.9] liters/1.73 m^2; $P < 0.01$).

DISCUSSION

The i.v. administration of 2 g of cefoperazone over 15 min to normal subjects resulted in pharmacokinetic parameters similar to those in other reports of cefoperazone pharmacokinetics in normal subjects (4, 5, 11). The smaller values of Cl_s and Cl_r in the present study (means of 61.7 and 15.8 ml/min per 1.73 m^2, respectively, as compared with means of 78 to 85 and 18 to 25 ml/min per 1.73 m^2 in other studies [4, 5, 11]) are probably related to the larger AUCs in the present study which resulted from using the correction for elimination of cefoperazone during infusion (8). The smaller V_{dss}s in the present study [mean, 6.3 liter/1.73 m^2, as compared with 9.9 to 11 liter/1.73 m^2 in the other studies [4, 5, 11]) are also influenced by the larger AUCs. Furthermore, the V_{dss} value is smaller than that for V_d calculated by the area method (7) used in other studies. For example, the mean V_d calculated by the area method (excluding the correction for elimination) for normal subjects in the present study is 8.9 liters/1.73 m^2, as compared with a mean V_{dss} of 6.3 liters/1.73 m^2 for V_{dss} (with the correction for elimination).

TABLE 2. Cefoperazone pharmacokinetics in normal subjects and patients with cirrhosis after a 2-g i.v. infusion over 15 min[a]

Patients	Peak serum concn (μg/ml)	$t_{1/2\beta}$ (h)	Cl_s (ml/min per 1.73 m^2)	Cl_r (ml/min per 1.73 m^2)	Renal excretion (% i.v. dose)	V_{dss} (liters/1.73 m^2)
Normal						
1	215	1.8	55.6	18.7	26	6.7
2	216	1.8	56.1	12.0	17	6.4
3	203	1.5	68.1	15.3	19	7.8
4	227	1.0	85.9	17.7	18	5.7
5	345	1.5	44.6	10.6	18	4.1
6	228	1.6	59.9	20.3	27	6.9
Mean ± SE	239 ± 21.5[b]	1.5 ± 0.1[c]	61.7 ± 5.7	15.8 ± 1.6	21 ± 2[b]	6.3 ± 0.5[b]
Cirrhotic						
1	206	3.5	55.6	46.6	60	12.7
2	175	9.9	19.2	14.6	59	15.1
3	135	2.8	86.0	NA	NA	14.3
4	122	5.0	32.7	12.8	32	13.3
5	123	2.3	89.0	46.6	51	16.1
6	82	3.5	95.8	NA	NA	23.8
Mean ± SE	141 ± 17.9[b]	4.5 ± 1.1[c]	63.1 ± 13.1	30.2 ± 9.5	50 ± 6[b]	15.9 ± 1.7[b]

[a] Cl_r and renal excretion measured 0 to 8 h and 0 to 12 h after administration of an i.v. dose in normal subjects and patients with cirrhosis, respectively. SE, Standard error; NA, not available.
[b] $P < 0.01$.
[c] $P < 0.05$.

Cefoperazone excretion is not impaired in patients with renal insufficiency (1, 3); however, hepatobiliary disease has been reported to reduce cefoperazone excretion (4; 21st ICAAC, abstr. no. 755; 21st ICAAC, abstr. no. 756). In the present study, patients with severe liver disease demonstrated significantly lower peak serum concentrations, significantly longer serum $t_{1/2\beta}$s, larger renal excretion, and larger V_{dss}s for cefoperazone as compared with those for normal subjects. Lower peak serum levels in patients with cirrhosis were probably related to a larger V_{dss}. The V_{dss} was apparently larger, secondary to ascites and lower serum protein binding of cefoperazone (normally 87 to 90%) that occurs in hepatic disease with its associated hypoalbuminemia and hyperbilirubinemia (5, 10). The V_{dss} of cefoperazone for patients with cirrhosis in the present study (mean, 15.9 liters/1.73 m^2) was larger than the V_d in patients with hepatic disease reported by Wheeler et al. (21st ICAAC, abstr. no. 755) (mean, 0.15 liters/kg, equivalent to 10.5 liters in a 70-kg person) and Cochet et al. (4) (mean, 11.7 liters). However, neither of these latter two studies mentioned the presence or absence of ascites or hypoalbuminemia.

In the present study, longer $t_{1/2\beta}$s of cefoperazone in the patients with cirrhosis were probably secondary to their severe hepatic dysfunction and larger V_{dss}s (2). However, the $t_{1/2\beta}$s were only minimally to moderately prolonged, except in a patient with a serum creatinine level of 2.1 mg/dl, whose $t_{1/2\beta}$ was 9.9 h. The patients with cirrhosis were significantly older (mean age, 47 years) than normal subjects (mean age, 27 years) ($P < 0.01$), and some of the older, chronically ill patients with cirrhosis with apparently normal serum creatinine levels (e.g., 1.2 mg/dl) probably had lower creatinine clearances than did the normal subjects. The renal excretion of cefoperazone was significantly larger in patients with cirrhosis (mean, 50%) as compared with normal subjects (mean, 21%), in agreement with the study by Cochet et al. (4) which showed a significantly larger renal excretion of cefoperazone in patients with hepatic disease (mean, 79%) as compared with normal subjects (mean, 24%). Therefore, as determined in the present study, patients with concomitant hepatic and renal dysfunction would be expected to have the longest $t_{1/2\beta}$s. The $t_{1/2\beta}$s of cefoperazone in patients with hepatobiliary disease reported by Cochet et al. (4) (mean, 4.3 h), Wheeler et al. (21st ICAAC, abstr. no. 755) (mean, 4.7 h), and Craig et al. (21st ICAAC, abstr. no. 756) (range, 3.4 to 7.1 h) were similar to that obtained in the present study (mean, 4.5 h). However, only Craig et al. (21st ICAAC, abstr. no. 756) mentioned renal function, and this was described simply as "relatively normal."

In summary, although mild to moderate im-

pairment of cefoperazone excretion occurs in patients with severe liver disease, marked impairment of excretion of the drug appeared to occur in only one patient with concomitant hepatic and renal dysfunction. In patients such as these, adjustment of the cefoperazone dose may be necessary.

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