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Pharmacology of Cefaclor in Normal Volunteers and Patients with Renal Failure

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After a 500-mg dose of cefaclor, the mean peak plasma level was 12.4 μg/ml and after a 250-mg dose it was 5 μg/ml in normal volunteers. Food intake significantly reduced absorption. Probenecid prolonged plasma levels. Mean plasma half-life in normal volunteers was 0.8 h. Only about 50% of the dose was excreted in the urine within 4 h in normal volunteers. Plasma half-life in patients with renal insufficiency was only about 3 h, which suggests that cefaclor may be eliminated by nonrenal mechanisms in humans. Urinary levels of cefaclor were adequate to inhibit susceptible pathogens even in patients with moderately severe renal failure. Plasma half-life during hemodialysis was 2.1 h and rose to 2.8 h after dialysis.

Cefaclor, 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid, is a new oral cephalosporin antibiotic that is structurally related to cephalexin. Cefaclor has been reported to be more active in vitro than cephalexin against *Enterobacteriaceae* and *Haemophilus influenzae*, but these drugs have similar activity against *Staphylococcus aureus* and other gram-positive cocci (1, 10–13). The present investigation was undertaken to determine the levels of cefaclor in the serum and urine of normal individuals, patients with various degrees of compromised renal function, and anephric patients during and after hemodialysis.

MATERIALS AND METHODS

Plasma levels of cefaclor were determined in crossover studies in five normal male volunteers, 28 to 40 years of age, and in patients with varying degrees of renal functional impairment. Each normal subject received a single oral dose of each of the following: 250 mg (3.0 to 4.1 mg/kg) and 500 mg (6.1 to 8.2 mg/kg) of cefaclor after an overnight fast, 500 mg of cefaclor within 0.5 h after a standard breakfast (juice, two eggs, toast, and coffee), and 500 mg of cefaclor while fasting, preceded 0.5 h before by 1.0 g of probenecid. Patients with varying degrees of renal functional impairment received 500 mg (4.7 to 8.2 mg/kg) of cefaclor when fasting. Anephric patients received this dose (6.3 to 9.3 mg/kg) immediately before starting hemodialysis. Cefaclor was provided by Eli Lilly & Co., Indianapolis, Ind., in 250-mg capsules. Patients were hemodialyzed on a Travenol RSP dialysis machine for 5 to 6 h (flow, 200 to 240 ml/min) with an EX23 dialyzer cartridge (thickness, 18 μm; surface area, 0.8 m^2, Extracorporeal Medical Specialties, Inc.). Heparinized samples of blood were obtained at 0.5, 1, 2, 3, and 4 h from normal volunteers and, in addition, at 6 to 8 h from those with renal insufficiency after administration of cefaclor. None had received antibiotics in the previous 2 weeks and each gave informed consent.

All volunteers provided specimens of urine by voiding before receiving a dose of cefaclor; patients with abnormal renal function provided urine over a 6-h interval, and normal volunteers provided 4-h urine collections. Plasma was immediately separated at 4°C, and both plasma and urine were immediately stored at −70°C until the time of assay. Stock standard solutions were prepared daily by dissolving standard cefaclor powder in phosphate buffer (pH 4.5). Standard concentrations (0.63 to 20 μg/ml) were prepared in plasma for plasma levels and in phosphate buffer (pH 4.5) for urine levels. Standards were frozen simultaneously with the plasma and urine samples. The concentrations of cefaclor in plasma and urine were determined by a modification of the agar-diffusion method of Wick, with the use of paper disks (9). Antibiotic medium 1 (Difco Laboratories) was used as the agar to measure cefaclor levels; *Bacillus subtilis* was the assay species; and the minimal level of cefaclor that could be detected by this method was 0.63 μg/ml.

Levels of cefaclor in plasma decreased with first-order kinetics after the peak when the logarithms of the concentrations were plotted against time. The half-life ($T_{1/2}$) of cefaclor in plasma was calculated from the formula: $T_{1/2} = \ln 2/m$, where m (calculated by the method of least squares) represents the rate constant of drug elimination from plasma (6).

RESULTS

Normal volunteers. In volunteers with normal renal function (endogenous creatinine clearance, 107 to 163 ml/min per 1.73 m^2) after 250

mg of cefaclor was taken in the fasting state, the mean peak plasma level (highest level measured during observation period) was 5.0 μg/ml (range, 4.4 to 5.8 μg/ml) (Table 1). The mean urine concentration was 684 μg/ml, and about 50% of the dose was excreted in a 4-h period. After 500 mg was taken while fasting, the mean peak plasma level achieved was 12.4 μg/ml (range, 8.6 to 15.3 μg/ml). The peak plasma level occurred usually 1 h after administration. The mean urine concentration was 1,533 μg/ml, and about 50% of the dose was excreted within 4 h. Probenecid did not significantly ($P > 0.05$ by t test for paired observations) increase the mean peak plasma level, which was 13.9 μg/ml (range, 10.7 to 16.1 μg/ml), but urine levels were significantly diminished ($P < 0.01$). The mean plasma $T_{1/2}$ among the five volunteers with normal renal function was 0.8 h, and probenecid significantly ($P < 0.01$) prolonged the $T_{1/2}$ to a mean of 1.3 h (t test for paired observations). However, this difference would probably be clinically insignificant. Postprandial administration reduced the mean peak plasma level by approximately 50% to 6.3 μg/ml (range, 4.0 to 8.9 μg/ml), delayed the peak plasma levels to 2 to 3 h after administration, and prolonged the duration of antibiotic levels in plasma.

Patients with renal functional impairment. Seven patients with creatinine clearances from 6.8 to 37.7 ml/min per 1.73 m^2 ingested 500 mg of cefaclor while fasting (Table 2). Peak plasma levels ranged from 12.1 to 23.2 μg/ml and were delayed usually to 2 to 4 h after administration. Despite severely impaired renal function, high levels of cefaclor were found in 6-h urine collections and ranged from 67 to 847 μg/ml. Plasma $T_{1/2}$ was prolonged in these patients with a range of 1.5 to 3.5 h.

Four anephric patients ingested 500 mg of cefaclor immediately before starting hemodialysis (Table 2). The mean peak plasma level was 19.7 μg/ml. The mean plasma $T_{1/2}$ on dialysis was 2.1 h and, after the same dose when dialysis had been discontinued, the $T_{1/2}$ rose to 2.8 h.

DISCUSSION

The mean peak plasma concentration of cefaclor in five volunteers with normal renal function was 12.4 μg/ml after a 500-mg fasting dose. After a dose of 250 mg, the mean peak level was approximately half this value (5 μg/ml), which was similar to that found by Korzeniowski et al. (4). The plasma levels of cefaclor are somewhat lower than serum concentrations of cephalexin after the same dose (4). Plasma levels of cefaclor were markedly reduced by eating, suggesting

TABLE 1. *Pharmacokinetics of cefaclor in normal volunteers*

Cefaclor dosage (mg)	Plasma cefaclor concn (μg/ml) at:					Mean peak plasma level (μg/ml)	Plasma $T_{\frac{1}{2}}$ (h)	0- to 4-h urine level (μg/ml)	% Urinary excretion
	0.5 h	1 h	2 h	3 h	4 h				
Fasting									
250	<0.6 – 5.1[a]	3.3 ± 0.7[b]	4.3 ± 0.7	<0.6 – 3.5	<0.6 – 1.4	5.0 ± 0.2[b] (4.4 – 5.8)[a]	—[c]	684 ± 107[b]	50.3 ± 16[b]
500	7.0 ± 2.2	11.5 ± 1.1	4.2 ± 0.6	1.7 ± 0.2	<0.6 – 1.6	12.4 ± 1.3 (8.6 – 15.3)	0.8 ± 0.1[b]	1,533 ± 391	51.4 ± 12.3
Fasting									
500 with probenicid	<0.6 – 8.1	13.2 ± 1.0	11.5 ± 1.3	6.6 ± 1.0	<0.6 – 5.9	13.9 ± 1.0 (10.7 – 16.1)	1.3 ± 0.1	596 ± 190	34.2 ± 5.8
Postprandial 500	<0.6 – 2.3	<0.6 – 6.0	6.1 ± 0.8	5.3 ± 0.6	<0.6 – 4.2	6.3 ± 0.8 (4.0 – 8.9)	ND[d]	ND	ND

[a] Range.
[b] Mean ± standard error.
[c] —, Not enough points for calculation.
[d] ND, Not done.

TABLE 2. *Pharmacokinetics of cefaclor (500 mg orally while fasting) in patients with renal insufficiency versus normal volunteers*

Creatinine clearance (ml/min per 1.73 m^2)	Peak plasma level (μg/ml)	Time to peak (h)	Urine concn (μg/ml)[a]	Plasma $T_{\frac{1}{2}}$ (h)
≥107(5 subjects)	12.4 ± 1.3[b]	0.5 – 1	1,533 ± 391[b]	0.8 ± 0.1[b]
37.7	20.5	2	847	1.5
16	18.0	4	189	2.1
16	22.1	3	77	2.8
12.5	12.1	4	312	3.0
12	19.9	2	67	3.5
8.6	15.4	2	152	2.4
6.8	23.2	1	258	3.3
0.0 (4 subjects)	19.7 ± 3.3	0.5 – 4		2.8 ± 0.8 (off dialysis) 2.1 ± 0.1 (on dialysis)

[a] Urine collection over 6 h in renal failure; 4 h with normal renal function.
[b] Mean ± standard error.

that the drug should be taken on an empty stomach.

Peak levels of cefaclor in patients with renal failure were higher than those found in volunteers with normal renal function after the same dose. Cephalexin also has been reported to attain higher peak levels in patients with compromised renal function (2, 5, 8). The reason for this may be slower renal excretion in patients with renal insufficiency. It is also possible that patients with renal dysfunction may have a smaller volume of distribution. Delays in peak levels of cefaclor were noted in patients with renal failure, as has been noted with cephalexin (2, 7).

High urine levels of cefaclor were found in individuals with normal renal function and, as with cephalexin (2, 5), urinary levels of cefaclor (67 to 847 μg/ml) adequate to inhibit susceptible urinary pathogens were still achieved despite substantial decreases in renal function. However, only about 50% in the present study and about 68% in another study (4) of the dose of cefaclor was excreted in the urine within 4 h after each dose in normal volunteers. In contrast, about 90% of cephalexin, which is not metabolized and eliminated only by the kidney, is recovered in the urine in this same period (4, 5). Some explanations for the lower urinary recovery of cefaclor are: (i) the intestinal absorption may be slower and less complete than cephalexin (14); (ii) cefaclor is inactivated at room temperature (4), so that cefaclor activity may decrease while urine is in the bladder; and/or (iii) cefaclor may be excreted by a nonrenal route or metabolized in vivo. In support of the last possibility is the relatively small difference in cefaclor plasma $T_{1/2}$ between patients with severe renal impairment and patients with normal renal function. For example, the mean plasma $T_{1/2}$ of cefaclor in volunteers with normal renal function was found to be 0.8 h, similar to the 0.6 h reported by Korzeniowski et al. (4). Anephric patients had a cefaclor $T_{1/2}$ of only 3 h. In marked contrast, cephalexin has a serum $T_{1/2}$ of about 0.8 h in in patients with normal renal function (2-5, 8) and up to 40 h (2, 3, 5, 8) in individuals with moderate to severe renal failure.

Studies with [^{14}C]cefaclor in rats and mice have indicated there is little metabolism of the drug (14). However, cefaclor is believed to be metabolized in dogs, which excrete only about 20% of unchanged antibiotic in the urine within 24 h after each dose (14). Our data also suggest that cefaclor may be similarly metabolized in humans.

In patients with creatinine clearances of ≤40 ml/min per 1.73 m^2, the plasma $T_{1/2}$ of cefaclor would be about 2 to 3 h (two to four times normal) and the dosage probably could be reduced to one-third to one-half of the usual maintenance dose. Patients with creatinine clearances of ≥40 ml/min per 1.73 m^2 would probably not require dose modification. Hemodialysis caused a minimal fall in plasma $T_{1/2}$ and would probably make further doses unnecessary.

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