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Failure of Probenecid to Alter the Pharmacokinetics of Ceforanide

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This investigation evaluated the effect of probenecid on ceforanide concentrations in eight healthy volunteers. Each volunteer was given 1 or 2 g of ceforanide either alone or with 1 g of probenecid. Concentrations of ceforanide in plasma, urine, and saliva were then measured. Probenecid did not alter the plasma concentrations of ceforanide, nor did it affect the urinary excretion of this agent. Ceforanide was not secreted into saliva in any detectable amount either when administered alone or with probenecid. It is not clear why probenecid has a negligible effect on ceforanide concentrations in plasma. It may be that tubular secretion plays less of a role in the excretion of ceforanide than expected, or that the physical properties of ceforanide prevent probenecid from affecting its excretion.

Probenecid has been shown to alter the pharmacokinetics of the penicillin and cephalosporin compounds (3–6, 9), mainly through competitive inhibition of the secretion of these antimicrobial agents within the renal tubules. Based on this principle ceforanide, a new, long-acting, semisynthetic cephalosporin, has been used with probenecid to treat life-threatening infectious diseases (2). We undertook this investigation to determine the effects of probenecid on plasma, urinary, and salivary concentrations of ceforanide. Since earlier investigations have suggested that ceforanide is excreted by glomerular filtration and tubular secretion, one would expect that probenecid would increase levels of ceforanide in plasma, as it has the levels of other cephalosporins (7).

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MATERIALS AND METHODS

Subjects. Eight healthy volunteers, three men and five women, aged 24 to 55 years with a mean age of 37.9 years, were randomly assigned to a drug protocol after voluntary, written consent was obtained. Each subject was screened with history and physical examination. Laboratory parameters of hematological, hepatic, and renal function were determined for each subject.

Antibiotics. Ceforanide (BL-S786R) was provided by Bristol Laboratories (Syracuse, N.Y.) as a lyophilized salt.

Probenecid. Commercially available 500-mg tablets of probenecid were utilized.

Investigation. Each of the subjects was randomly assigned to receive either 1 g of ceforanide intramuscularly and 2 weeks later 2 g of ceforanide intramuscularly with probenecid taken orally or 2 g of ceforanide intramuscularly alone and 2 weeks later 1 g of ceforanide intramuscularly with probenecid taken orally. In all cases ceforanide and probenecid were administered simultaneously. Four subjects were assigned to each dosing regimen.

Plasma samples for ceforanide concentrations were obtained immediately before administration of the drug, at 30 min, and at 1, 2, 3, 5, 9, 12, and 24 h after the injection. Specimens of saliva were obtained each time a blood specimen was drawn. We obtained 3 ml of saliva for each sample. Production of saliva was stimulated by having each subject chew on paraffin wax. All urine during the following time intervals was collected for determination of ceforanide concentrations: 0 to 4, 4 to 6, and 6 to 12 h after administration of 1 g of ceforanide, and at 0 to 2, 2 to 4, 4 to 6, and 6 to 12 h after the administration of 2 g of ceforanide.

Antibiotic assay. Ceforanide concentrations in plasma, urine, and saliva were determined by the cup-plate method using *Klebsiella pneumoniae* (Bristol A-9977) as a test organism.

Data analysis. Plasma concentrations of ceforanide were plotted against the times at which they occurred and compared statistically by the Student *t* test. Peak plasma levels and time of occurrence were tabulated. To calculate the half-life of ceforanide, the terminal slope of logarithm of the plasma concentration versus time curve was determined by linear regression. The area under the plasma concentration versus time curve (AUC) was also determined. Plasma clearance (Cl_p), corrected for body weight, was calculated by $Cl_p = (1.73 \times D)/(\text{AUD} \times \text{BSA})$, where D is ceforanide dose and BSA is subject body surface area in square meters. BSA was calculated from subject height and weight using Boyd's formula (1). Urine

concentrations for each time interval were compared by the Student t test.

RESULTS

Figure 1 shows the plasma concentration of ceforanide attained on the 1- and 2-g dosage regimens with and without administration of probenecid. There was no apparent difference in the ceforanide concentrations within either regimen. Compared by means of the Student t test, the concentrations at each time interval were not statistically different, each showing a P value of >0.15.

Table 1 presents data for urinary excretion of ceforanide during the first 12 h after drug administration for the 1- and 2-g dosage regimens, both with and without probenecid. Collection time periods ranged from 2 to 6 h. Concentration for each period within corresponding regimens did not appear to vary and did not differ statistically when compared by the Student t test, yielding P values of >0.15.

Concentrations of ceforanide in saliva were less than 0.5 μg/ml, whether ceforanide was administered alone or with probenecid.

Table 2 shows the maximal concentrations, the times at which they occurred, and the half-life of ceforanide for each regimen. The area under each of the curves in Fig. 1 and the plasma clearance for each regimen are also shown in Table 2.

DISCUSSION

Ceforanide has a half-life of 3.36 h. It has been estimated that 50% of ceforanide is excreted by glomerular infiltration and 50% by tubular secre-

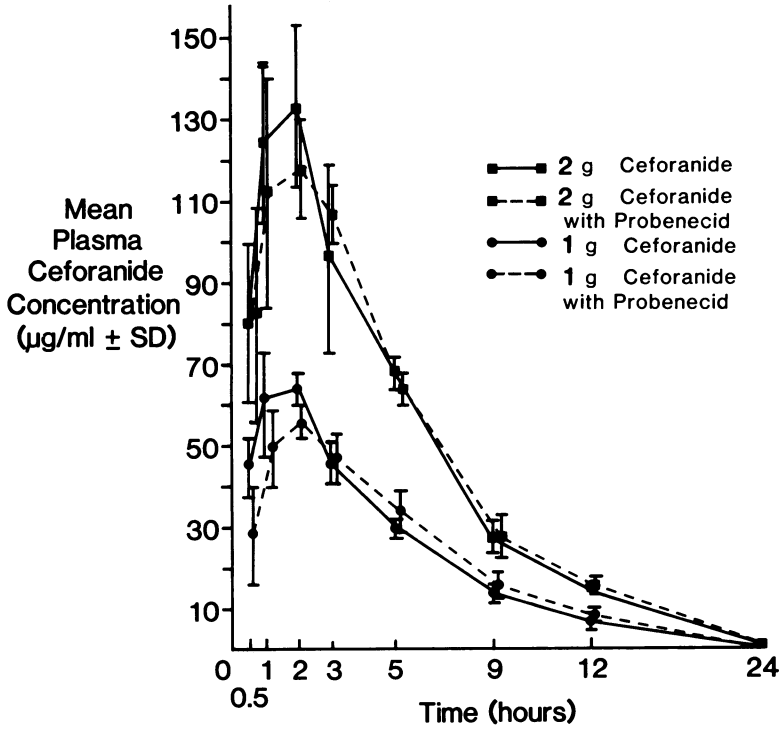

FIG. 1. *Mean plasma concentration of ceforanide versus time after administration of 1 and 2 g of ceforanide with or without probenecid.*

TABLE 1. *Mean amount of ceforanide recovered in the urine at various intervals*

Dosage regimen	Mean amt (g)[a] of ceforanide recovered at h:				
	0–2	0–4	2–4	4–6	6–12
Ceforanide (1 g)		0.55 (55)		0.20 (75)	0.21 (96)
Ceforanide (1 g) with probenecid		0.41 (41)		0.22 (63)	0.16 (79)
Ceforanide (2 g)	0.50 (25)		0.48 (49)	0.44 (71)	0.52 (97)
Ceforanide (2 g) with probenecid	0.64 (32)		0.56 (60)	0.40 (80)	0.38 (99)

[a] Values in parentheses are urine excretion expressed as the cumulative percentage of dose administered.

TABLE 2. *Pharmacokinetic parameters of ceforanide after 1- and 2-g dosages with and without probenecid*

Probenecid dose (g)	Ceforanide dose (g)	C_{max}[a] (μg/ml)		T_{max}[b] (h)		$T_{1/2}$[c] (h)		AUC[d] (μg·h/per ml)		Cl_p[e] (ml/min per 1.73 m^2)
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
0	1	66	6	1.25	0.50	3.22	0.59	383	—[f]	42.2
										4.2
1	1	56	4	1.75	0.50	3.67	0.58	396	—	39.3
										4.8
0	2	140	19	1.75	0.50	3.20	0.67	806	—	38.4
										3.6
1	2	124	13	1.75	0.96	3.33	0.39	879	—	36.7
										3.3

[a] C_{max}, Peak plasma levels.
[b] T_{max}, Time of occurrence of C_{max}.
[c] $T_{1/2}$, Half-life of ceforanide.
[d] AUC, Area under the curve.
[e] Cl_p, Plasma clearance.
[f] —, Not applicable.

tion (7). It was postulated, therefore, that probenecid would increase plasma concentration of ceforanide through its competitive inhibition with ceforanide in the renal tubules. The therapeutic importance of this blocking action was suggested when the combination of ceforanide and probenecid was used to treat infective endocarditis (2).

From the data obtained in our study, however, probenecid does not appear to affect the plasma concentrations of ceforanide or the urinary excretion of this antimicrobial agent. One explanation for this would be that tubular secretion of ceforanide plays a less significant role in the excretion of ceforanide than previously postulated. Another possible explanation would be that the chemical composition of ceforanide which demonstrates two pK_a's, one acidic and one basic, may prevent the tubular secretion by transport mechanisms with which probenecid normally competes (F. K. Lee, Bristol Laboratories, personal communication).

Data from our study also indicate that ceforanide is not secreted into saliva in any significant amount even when administered with probenecid. This may be significant since it has been shown that cephalosporins do not affect the meningococcal carrier state or eradicate oral gonococcal infections because of poor salivary concentrations (8).

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