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Effect of Probenecid on the Blood Levels and Urinary Excretion of Cefamandole

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Two oral 0.5-g doses of probenecid given 7 and 1 h before a single 1-g intramuscular dose of cefamandole resulted in higher serum levels of cefamandole than when cefamandole was given alone: 37 versus 20 μg per ml of serum, respectively. Cefamandole was not measurable (<0.3 μg/ml) at 8 h when it was given alone, whereas an average 8-h value of 2.9 μg/ml was obtained after pretreatment with probenecid. By prolonging the duration of these high cefamandole levels, probenecid should permit the treatment of more serious clinical infections, including those due to relatively resistant organisms, or permit a reduction in either the dosage of cefamandole or the frequency of administration.

Probenecid has been shown to competitively inhibit the excretion of penicillin and cephalosporins by the tubules of the kidneys (6). In a previous publication, we reported the pharmacokinetics of cefamandole after intramuscular (i.m.) and intravenous injection (3). The data in this paper illustrate the effect of probenecid on the serum levels and urinary excretion of cefamandole.

MATERIALS AND METHODS

Antibiotic. The lithium salt of cefamandole as standard powder was supplied in 20-mg ampoules by Eli Lilly & Co., Indianapolis, Ind. The cefamandole for clinical use, CT-2883-4F, was cefamandole nafate furnished as 1 g of cefamandole activity per ampoule.

Subjects. Twelve male volunteers between the ages of 25 and 55 years were admitted to the study after being screened by history and physical examination and laboratory determination of blood, renal, and liver function. Informed written consent was obtained.

Injection of antibiotic. For i.m. injection, 3 ml of distilled water was added to each 1-g ampoule of cefamandole. The injection was given in the gluteal muscle through a 1.5-inch (ca. 3.8-cm) 20-gauge needle.

Probenecid. Commercially available tablets of probenecid (Benemid, Merck Sharp & Dohme, West Point, Pa.) were administered orally in a dose of 0.5 g 7 and 1 h before the injection.

Serum assays. Blood samples were drawn before and at intervals after the administration of single doses of cefamandole (see Table 1). The blood samples were centrifuged and the sera were frozen until assayed. Serum concentrations were measured using the *Bacillus subtilis* cup plate method (4).

Urine assays. Urine was collected at the intervals shown in Table 2. The urines were assayed by using an Elanco Autoturb (Elanco Products Co., Indianapolis, Ind.) with a *Klebsiella* strain as the indicator organism.

Statistical analysis. A paired *t* test was used to test the hypothesis that the means for both treatment groups are the same versus the hypothesis that these means are different. This pairing was necessary since each patient in this study received each of the study medications.

RESULTS

Figure 1 shows the average cefamandole blood levels achieved after the i.m. injection of 1 g of cefamandole alone compared with those obtained when 1 g of cefamandole was given to the same subjects after they had received probenecid orally. Figure 2 illustrates the alteration of cefamandole excretion by probenecid.

Probenecid administered orally in doses of 0.5 g every 6 h (for two doses) almost doubled the peak blood levels obtained after administration of 1 g of cefamandole: 37 and 20.4 μg/ml, respectively. The half-life was obviously prolonged by probenecid: 1.1 to 2 h; and at 8 h cefamandole could not be assayed in the blood after cefamandole alone, but after cefamandole plus probenecid, 2.9 μg/ml was found.

The higher and more prolonged levels seen with prebenecid plus cefamandole are related to the delay in excretion of cefamandole by the effect of probenecid on the kidney tubules. In Fig. 2 it is apparent that more cefamandole appeared in the urine during the first and second 2-h collection periods after cefamandole

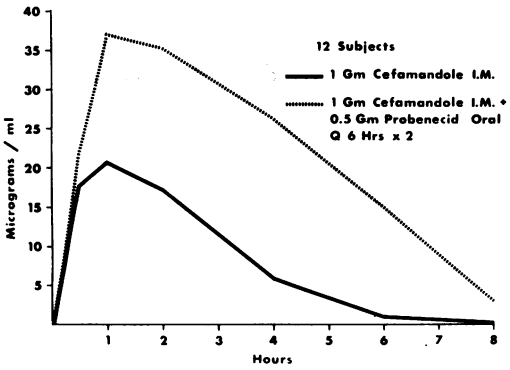

FIG. 1. *Effect of probenecid on cefamandole blood levels.*

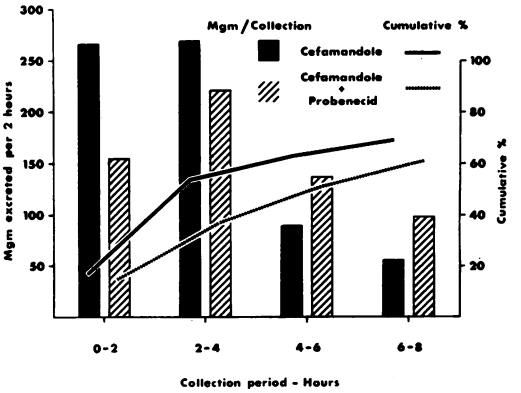

FIG. 2. *Urinary excretion of cefamandole.*

TABLE 1. *Concentrations of cefamandole in serum after i.m. administration*

Subject	Concn (μg/ml) in serum at h:						
	0	0.5	1	2	4	6	8
Cefamandole (1 g)							
AB	0	25	16	10	3.5	1.2	0.4
RD	0	47.6	26.6	14.3	2.5	0.5	<0.3
ME	0	29.3	43.5	21.4	2.5	0.4	<0.3
HG	0	17.1	16.7	17.6	4.9	0.8	<0.3
JH	0	9	9	9.7	6.3	2.2	0.6
TH	0	4.4	12.3	14.4	2.9	0.8	<0.3
RM	0	5.8	14	15.1	6.2	2.2	1.1
AP	0	22.4	40.2	20.4	6.2	1.6	1.2
DW	0	19.5	20.1	13.1	4	0.7	<0.3
RB	0	4.1	7.1	20.1	6	0.9	<0.3
PM	0	23.6	26.2	14.9	2.3	0.5	<0.3
ES	0	5.9	13.3	12.6	25.3	0.6	<0.3
Mean	0	17.8	20.4	15.3	6.1	1	<0.3
SD[a]	0	13	11.7	3.8	6.3	0.6	0.4
Cefamandole (1 g) + probenecid[b]							
AB	0	24.3	45.3	50.4	86.4	26.3	8.3
RD	0	23.8	14.8	6.2	1.5	0.3	<0.3
ME	0	84.2	93.8	54.7	27.1	7	2.5
HG	0	2.3	18.5	24.2	24.9	19	3.6
JH	0	7.9	25.5	28.4	10.8	2.5	<0.3
TH	0	9.5	31.5	32.7	20.2	9.5	2.9
RM	0	9.4	13	13	7.3	2.9	1
AP	0	23.1	62.8	50.9	16.9	2	0.4
DW	0	8.4	21.6	37.3	25.6	11.6	3
RB	0	10.4	19.7	30.9	24.2	10.8	3.3
PM	0	19.7	48.5	37.9	32.1	17.2	5.9
ES	0	28.4	48.6	57.1	67	83	3.8
Mean	0	21	37	35.3	28.7	16	2.9
SD	0	21.6	24	16.2	24.5	22.5	2.4
Paired *t*-value		0.55	3.31	4.29	3.47	2.28	3.33
P-value[c]		0.598	0.007	0.001	0.005	0.043	0.007

[a] SD, Standard deviation.
[b] A 0.5-g dose of probenecid 7 and 1 h before cefamandole injection.
[c] Two-tailed probability value.

alone than when probenecid was present. During the third and fourth 2-h collection periods, the reverse was true: more was excreted in the urine after cefamandole plus probenecid than after cefamandole alone. This delay in excretion may be related both to the prolongation of higher cefamandole blood levels after probenecid and to a progressive reduction in probenecid effect, as it is also removed by the kidney.

The individual blood levels (Table 1) and urinary excretion of cefamandole (Table 2) with and without probenecid are shown for closer scrutiny.

DISCUSSION

Probenecid is an organic acid that has a relatively high affinity for the renal tubular transport system and is readily secreted with subsequent rapid reabsorption. This "recirculation" accounts for the prolonged action of probenecid (6). Since other organic acids, such as the penicillins or cephalosporins, are excreted by the same tubular mechanism, the administration of probenecid competitively blocks their elimination by the kidney tubules (1). Renal clearance values for the penicillins and cephalosporins by the kidney under the influence of probenecid approach the glomerular filtration rate.

Fong et al. showed a half-life of approximately 50 min for cefamandole administered i.m. (2). These same authors reported that the renal clearance of cefamandole was 257 ml/min per 1.73 m^2.

Using the same formula, we found a renal clearance of 229 ml/min per 1.73 m^2 during the 2- to 4-h and 4- to 6-h urine collection periods.

TABLE 2. *Concentrations of cefamandole in urine after i.m. administration*

Subject	0-2 h			2-4 h			4-6 h			6-8 h		
	μg/ml	Total vol (ml)	Total mg	μg/ml	Total vol (ml)	Total mg	μg/ml	Total vol (ml)	Total mg	μg/ml	Total vol (ml)	Total mg
Cefamandole (1 g)												
AB	1,365	230	314	844	250	211	355	210	75	145	180	26
RD	2,973	160	476	2,426	90	218	406	75	30	197	90	18
ME	4,800	80	384	3,876	50	194	344	60	21	251	60	15
HG	1,037	100	104	2,205	120	265	2,139	110	235	1,486	80	119
JH	750	190	143	2,205	150	353	1,564	110	172	392	110	43
TH	3,857	95	366	2,459	90	221	719	50	36	356	80	28
RM	1,780	115	205	1,898	120	228	800	130	104	313	90	28
AP	797	240	191	2,503	100	250	406	160	65	217	160	35
DW	1,520	210	319	3,050	60	183	810	80	65	267	60	16
RB	1,185	100	119	4,153	110	457	1,289	100	129	188	60	11
PM	938	300	281	1,313	260	341	492	170	84	267	60	16
ES	3,234	90	291	3,189	65	207	970	70	68	356	60	21
Mean	2,020	159	266	2,510	122	261	858	110	90	370	91	31
SD[a]	1,356	73	115	958	60	82	546	46	63	360	41	29
Cefamandole (1 g) + probenecid[b]												
AB	63	140	9	438	180	79	500	170	85	500	180	90
RD	813	310	252	500	280	140	1,039	240	249	1,477	150	222
ME	750	220	165	500	240	120	1,297	70	91	1,092	40	44
HG	250	100	25	1,125	160	180	1,799	80	144	1,211	90	109
JH	313	250	78	1,250	180	225	1,053	130	137	1,039	110	114
TH	1,000	180	180	3,749	80	300	1,105	115	127	1,053	65	68
RM	3,550	10	36	938	180	161	1,105	110	122	1,013	90	91
AP	2,179	150	327	1,920	85	163	1,320	100	132	969	80	78
DW	750	190	143	1,680	210	353	1,590	100	159	781	50	39
RB	1,063	110	117	2,511	170	427	1,158	130	151	969	100	97
PM	2,238	120	269	1,000	180	180	1,026	90	92	1,013	130	132
ES	2,961	85	252	2,596	120	312	1,053	150	158	938	100	94
Mean	1,327	155	154	1,517	172	221	1,170	124	137	1,005	99	98
SD	1,130	81	105	1,017	58	105	321	46	44	231	40	47
Paired *t*-value		3.146			1.342			2.088			4.278	
P-value[c]		0.0093			0.2069			0.0608			0.0013	

[a] SD, Standard deviation.
[b] A 0.5-g dose of probenecid 7 and 1 h before cefamandole injection.
[c] Two-tailed probability value.

Probenecid produced a decrease in renal clearance of cefamandole to 57 ml/min per 1.73 m^2 during these same collection periods. No attempt was made to establish the maximal effective dose of probenecid required to block the tubular transport of cefamandole. The usual adult dose of probenecid, 0.5 g every 6 h, has been shown to adequately block penicillin (1). This clearance rate of 57 ml for cefamandole when given with probenecid is similar to the rate of 75 ml reported by Kirby and Regamey for cefazolin without probenecid (5).

When probenecid is used, approximately 2% of the patients will have some noticeable degree of gastrointestinal irritation; hence, caution should be exercised if probenecid is administered to patients with known peptic ulcer (1). In addition, skin rash has been reported in 2 to 4% of those taking probenecid (1). Thus, it is difficult to differentiate the etiology of hypersensitivity should probenecid be given with another medication, a diagnostic dilemma not uncommon with the polytherapy of today.

In conclusion, the administration of probenecid, 0.5 g every 6 h orally, with cefamandole will almost double the blood levels and prolong the duration of therapeutic levels of cefamandole by competitively blocking the renal tubular transport of cefamandole.

The higher and more prolonged blood levels of cefamandole associated with probenecid should permit the treatment of more serious clinical infections, including those due to relatively resistant organisms, or a reduction either in dose or in frequency of administration.

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