ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1984, p. 944–946
0066-4804/84/120944-03$02.00/0

Vol. 26, No. 6

Decreased Biliary Excretion of Cefamandole After Percutaneous Biliary Decompression in Patients with Total Common Bile Duct Obstruction

JOE U. LEVI, OCTAVIO V. MARTINEZ,* THEODORE I. MALININ, ROBERT ZEPPA, ALAN LIVINGSTONE, DUANE HUTSON, AND PATRICIA CALHOUN

Department of Surgery, University of Miami School of Medicine, Miami, Florida 33101

Received 19 July 1984/Accepted 24 September 1984

The biliary penetration of cefamandole was studied in six patients with total biliary obstruction before and after placement of a transhepatic bile drainage catheter. Biliary levels of cefamandole remained depressed even when the drug was administered as late as 7 days after decompression of the biliary tract.

Cefamandole is excreted in high concentrations in unobstructed bile. Maximum biliary levels of this agent reach approximately 340 μg/ml at nearly 2 hours after administration of a 2-g dose intravenously (2). In the presence of a biliary obstruction, however, hepatic excretion of this and other cephalosporins is markedly inhibited (5, 6). We have noted previously that in patients with total obstruction the hepatic clearance of another β-lactam agent, aztreonam, appeared to have been impaired for as long as several days after reestablishment of normal biliary flow (4). It was of interest, therefore, to determine whether a similar impairment in the biliary secretion of cefamandole persists after biliary decompression in patients with total obstruction. The present study describes the degree of penetration of cefamandole into the bile of six patients with total common bile duct obstruction and at various times after reestablishment of biliary drainage.

Two male and four female patients ranging in age from 38 to 62 years were entered into the study. All patients had total obstruction of the biliary tract at the time of the study as demonstrated by transhepatic cholangiography. The postoperative diagnosis of all six patients was pancreatic carcinoma. All of the subjects had normal renal function (serum creatinine, <1.3 mg/100 ml) but most had elevated liver function test values as a consequence of their biliary disease. Results of renal and hepatic function tests from serum samples collected at the time of drug administration are shown in Table 1. Written consent was obtained from all subjects.

The patients were given a single 2-g dose of cefamandole intravenously either before or after biliary decompression as indicated below. The drug was dissolved in 100 ml of 5% dextrose in water and administered within 10 min by means of an infusion drip. Decompression was accomplished by percutaneous placement of a catheter into the hepatic bile ducts. Immediately after insertion of the catheter and reestablishment of the biliary flow, samples of the effluent bile and blood from a peripheral vein were collected simultaneously. Similar samples then were collected after 0.25, 0.50, 1, 2, 3, and 4 h. For three of the patients, the study was repeated on subsequent days. Blood and bile samples were collected as before except that the initial sample pair was obtained 0.25 h after the administration of the drug. The bile catheters were maintained open at all times after the initial decompression of the biliary tract. Serum and bile samples were kept frozen (−70°C) until assayed for cefamandole concentrations. This was done by a microbiological agar diffusion method (3) with *Bacillus subtilis* ATCC 6633 as the indicator strain. All bile samples were serially diluted in phosphate buffer (pH 6) before being assayed. The limits of sensitivity of this assay for cefamandole in serum and bile was 0.25 and 0.5 μg/ml, respectively. Bile samples also were assayed for blood content by a quantitative colorimetric procedure for hemoglobin content according to the instructions of the manufacturer (Sigma Chemical Co.; technical bulletin no. 525, August 1982). The amount of blood in the bile was calculated from a standard reference curve with blood from each patient in pooled human bile. In those samples in which blood was detected, values for cefamandole concentrations were corrected by subtracting the amount of drug present in the blood contaminating the sample. Patients, 1, 2, and 3 were given cefamandole 10 min (patient 3) to 1 h before biliary decompression. Patients 4, 5, and 6 were given the drug 1 h after biliary decompression and then again after 24, 48 (patient 4), 96 (patient 5), and 7 days (patient 6).

Maximum biliary concentrations of cefamandole ranged from 4.8 to 47.5 μg/ml at 0.25 to 3.0 h after drug infusion (Table 2). The Mean ± standard deviation for the three patients given cefamandole before biliary decompression was 5.9 ± 1.7 μg/ml. The mean ± standard deviation for the three patients given the drug 1 h after decompression was higher (18.7 ± 10.3 μg/ml) and was significantly higher (28.7 ± 18.6 μg/ml; $P < .05$; two-sample t-test) when cefamandole was administered 24 h later. Biliary levels of cefamandole at 4 h after drug administration ranged from <0.5 to 12.9 μg/ml (mean, 4.5 μg/ml). Of the three patients who were studied on separate days, only one (patient 6) showed an increase in the maximum biliary concentration of cefamandole with increasing time between biliary decompression and drug administration. In contrast to previous studies involving the use of T tubes in patients (2, 3), cefamandole was not concentrated in the bile of our subjects. In almost all patients, maximum levels of cefamandole in the bile were lower than both the corresponding peak serum level and the simultaneous concentration of the drug in the serum. In the one patient

* Corresponding author.

TABLE 1. Hepatic and renal function test values form six patients with total common bile duct obstruction at various times after biliary decompression

Patient no.	Sex	Age (yr)	Cefamandole infusion time[a] (h)	Serum chemistry at time of drug administration[b]				
				Bilirubin (mg/100 ml)	Alkaline phosphatase (U/liter)	SGOT (U/liter)	SGPT (U/liter)	Creatinine (mg/100 ml)
1	F	58	−1	9.3	299	142	104	0.5
2	F	38	−1	12.4	544	102	76	0.9
3	M	62	−0.2	14.6	1,575	257	140	1.0
4	M	42	+1	17.8	1,375	259	78	0.5
			+24	ND	ND	ND	ND	ND
			+48	10.7	990	122	49	0.8
5	M	62	+1	19.5	323	80	46	1.3
			+24	19.6	336	63	53	1.2
			+96	ND	ND	ND	ND	ND
6	M	47	+1	24.5	1,405	464	930	0.7
			+24	ND	ND	ND	ND	ND
			+168	7.4	637	280	710	0.7

[a] −, time before biliary decompression; +, time after decompression.
[b] Normal values: serum bilirubin, 0.1 to 1.3 mg/100 ml; alkaline phosphatase, 10 to 125 U/liter; serum glutamic oxaloacetic transaminase (SGOT), 0 to 50 U/liter; serum glutamic pyruvic transaminase (SGPT), 0 to 50 U/liter; creatinine, 0.5 to 1.5 mg/100 ml. ND, Not done.

studied 7 days postdecompression (patient 6), the maximum biliary level of cefamandole was slightly higher than the simultaneous serum concentration.

Reported mean peak levels of cefamandole in unobstructed bile are approximately 125 to 150 μg/ml per 1-g dose intravenously (1, 2) O. V. Martinez, J. Levi, T. Malinin, and R. Zeppa, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev., abstr. no. 709, 1983). In the present studies, the maximum biliary concentrations of cefamandole in patients with previous total biliary obstruction did not exceed 50 μg/ml even when the 2-g dose was administered as late as 7 days after biliary decompression. β-Lactam antibiotics penetrate into the bile via an active secretory mechanism within the hepatocytes (6). Our results suggest that in patients with total biliary obstruction, the hepatocytes do not recover full secretory capacity for this drug, and possibly for other cephalosporins as well, for up to several days after restoration of the biliary flow. The clinical implications of this phenomenon are unknown since it is not clear whether high biliary concentrations of antibiotics are of therapeutic significance (5). We recommend that patients with present or recent total biliary obstruction be excluded from human pharmacokinetic studies of the biliary excretion of cephalosporins or other antibiotics.

TABLE 2. Concentrations of cefamandole in serum and bile from patients with common bile duct obstruction and at various times after biliary decompression

Patient no.	Cefamandole infusion time[a] (h)	Cefamandole concn (μg/ml) at time (h) after drug administration:											
		Serum						Bile					
		0.25	0.5	1	2	3	4	0.25	0.5	1	2	3	4
1	−1	ND[b]	ND	43.7	17.6	9.0	6.3	ND	ND	<0.5	8.0	7.5	3.5
2	−1	ND	ND	27.4	10.5	6.6	3.8	ND	ND	2.4	4.8	0.7	<0.5
3	−0.2	63.7	38.5	32.5	11.5	7.0	8.9	<0.5	<0.5	3.8	5.0	4.7	1.6
4	+1	103	60.8	24.5	7.6	5.2	2.4	11.4	19.1	14.6	4.3	<0.5	<0.5
	+24	180	105	47.3	19.5	7.7	5.7	29.7	29.4	17.1	2.7	1.0	0.5
	+48	104	65.6	24.8	10.5	1.4	0.5	8.6	9.8	5.2	1.8	3.1	1.5
5	+1	116	96.4	76.4	57.9	40.8	37.2	<0.5	<0.5	7.2	8.9	28.9	11.8
	+24	126	100	70.9	43.4	29.5	20.3	40.1	46.8	47.5	21.4	10.2	12.9
	+96	275	73.0	54.9	30.7	18.4	9.8	7.4	20.4	17.9	12.3	9.6	5.8
6	+1	77.2	50.6	20.2	7.6	4.2	1.5	<0.5	8.2	8.1	1.8	0.8	<0.5
	+24	95.6	71.8	29.8	6.7	3.6	1.6	2.4	3.4	9.8	4.7	1.2	0.5
	+168	110	57.7	22.6	8.7	4.0	3.0	2.8	19.0	24.4	4.4	1.2	0.6

[a] −, Time before biliary decompression; +, time after decompression.
[b] ND, Not done.

This study was supported by the Eli Lilly Co., Indianapolis, Ind.

We acknowledge the assistance of Edward Russell, Jorge Guerra, and James Le Page of the Department of Radiology. We thank Patricia Buchanan for typing the manuscript and Maria Ramos and Phillip Valla for their technical assistance.

LITERATURE CITED

1. **Brogard, J. M., M. Pinget, J. P. Arnaud, M. Dorner, M. Adoff, and J. Lavillaureix.** 1981. E'tude experimentale et clinique de l'elimination biliaire de cefamandole. Pathol. Biol. (Paris) **29**:25–30.
2. **Levi, J., A. S. Livingstone, O. V. Martinez, R. Zeppa, T. Malinin, D. G. Hutson, and N. C. Einhorn.** 1980. Biliary concentrations of cefamandole and its use in biliary tract surgery. Scand. J. Infect. Dis. **25**(Suppl.):55–57.
3. **Lindahl, F., T. Kjaer, and V. F. Thomsen.** 1980. Excretion of cefamandole in bile. Scand. J. Infect. Dis. **25**(Suppl.):58–59.
4. **Martinez, O. V., J. Levi, and R. G. Devlin.** 1984. Biliary excretion of aztreonam in patients with biliary tract disease. Antimicrob. Agents Chemother. **25**:358–361.
5. **Quintiliani, R., M. French, and C. Nightingale.** 1982. First and second generation cephalosporins. Med. Clin. N. Am. **66**:183–197.
6. **Smith, B. R., and J. Le Frock.** 1983. Biliary tree penetration of parenteral antibiotics. *In* R. Quintiliani (ed.), Infections in surgery. Hartford Hospital, Hartford, Conn.