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Biliary Concentrations of Piperacillin in Patients Undergoing Cholecystectomy

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Piperacillin is a new semisynthetic, expanded-spectrum penicillin with marked activity against *Pseudomonas aeruginosa*. The biliary excretion of piperacillin was studied in patients undergoing cholecystectomy. Concentrations of piperacillin in common duct bile at 35 to 90 min postinfusion of 1-g doses ranged from 31 to 920 μg/ml, with a mean (±standard deviation) of 467 ± 363 μg/ml. Gallbladder piperacillin levels at 30 to 75 min postinfusion ranged from 2.2 to 80 μg/ml, with a mean of 27 ± 31 μg/ml. No correlation occurred with peak serum level of antibiotic, creatinine, bilirubin, or alkaline phosphatase. Significant amounts of piperacillin were excreted via the biliary system.

The pharmacokinetics of piperacillin {sodium 6-[D-(−)-α(4-ethyl-2,3-dioxo-1-piperazinyl carbonylamino)-α-phenylacetamido] penicillinate}, a new semisynthetic penicillin with an expanded spectrum against both gram-negative and gram-positive aerobes and anaerobes (5–7, 10) have been studied in patients with normal renal function (2, 8), in patients with stable mild to moderate renal failure (J. A. Giron, B. R. Meyers, and S. Z. Hirschman, submitted for publication) and in patients undergoing hemodialysis (3). It appears that nonrenal pathways of excretion affect the pharmacokinetics of piperacillin. The antimicrobial spectrum of piperacillin suggests its potential use in infections of the liver and biliary tract. We investigated the excretion of piperacillin in the biliary system of patients undergoing cholecystectomy.

MATERIALS AND METHODS

Five patients undergoing cholecystectomy for medical indications were studied. No patient had a biliary tract obstruction at the time of the study. The patients had cholelithiasis without clinical evidence of cholecystitis or cholangitis. All of the patients had normal serum bilirubin, aspartate aminotransferase, and alanine aminotransferase values. The five patients included four females and one male, ages 30 to 64 years. Every patient had a serum creatinine level of less than 1.8 mg/100 ml. All patients gave informed consent according to the institutional policy. Penicillin-allergic patients and pregnant patients were excluded.

The patients were prepared for cholecystectomy by standard procedures. At induction of anesthesia, 1 g of piperacillin was infused intravenously for 30 min. Samples of gallbladder and common duct bile were obtained when the gallbladder was removed and when the common duct was explored. The time after the beginning of infusion at which the samples were obtained was recorded. Serum samples were drawn over a 3-h interval after beginning the infusion.

Bile samples were mixed with 0.1 M phosphate buffer (pH 6) immediately to prevent piperacillin inactivation (A. Dornbush, personal communication). Blood samples were centrifuged, and the serum was collected. All samples were stored at −70°C until assayed for piperacillin concentration. Piperacillin concentrations were determined by the paper disk assay method, using *Sarcina lutea* 9341 as the test organism (4). Patient 5 had been given ampicillin, and, therefore *Pseudomonas aeruginosa* 3414 was used as the assay organism. Standard test assays performed with the two test organisms yielded similar results.

Every patient had a complete blood count and serum biochemical profile performed before and after the administration of piperacillin.

RESULTS

The serum concentrations of piperacillin after a 1-g intravenous dose are shown in Table 1. The mean (± standard deviation) peak level of piperacillin occurred at the end of the 30-min infusion and was 75.3 ± 46.6 μg/ml. Serum levels decreased rapidly so that by 3 h postinfusion the mean serum level was 11.1 ± 7.1 μg/ml.

Common duct and gallbladder biliary concentrations of piperacillin are shown in Tables 2 and 3, respectively. Piperacillin concentrations of bile samples from the common duct were quite high and exceeded gallbladder concentrations. Common duct levels of piperacillin at 35 to 90 min postinfusion ranged from 31 to 920 μg/ml, with a mean concentration during the 55-min period of 467.8 ± 363.4 μg/ml. Gallbladder levels at 30 to 75 min postinfusion ranged from 2.2 to 80 μg/ml, with a mean of 27.2 ± 31 μg/ml during the 45-min period.

Common duct bile levels of piperacillin did not correlate with peak serum levels of pipera-

TABLE 1. *Piperacillin levels in cholecystectomy patients*

Time (h)	Serum concn (μg/ml) in patients:					
	1	2	3	4	5	Mean ± standard deviation
0	0	0	0	0	0	0
0.25[a]	31	16	28	150	88	62.6 ± 56.2
0.5[a]	88	26.5	28	130	104	75.3 ± 46.4
1	44	20	14	70	46	38.8 ± 22.5
2	45.5	6.4	5.2	32	19	21.6 ± 17.2
3	5.9	4.0		16.8	17.5	11.1 ± 7.1

[a] During infusion.

TABLE 2. *Common duct bile concentrations of piperacillin*

Patient	Time of sample (min)	Bile concn (μg/ml)
1	90	480
2	60	920
3		
4	45	440
5	35	31
Mean ± standard deviation		467.8 ± 363.4

TABLE 3. *Gallbladder bile concentrations of piperacillin*

Patient	Time of sample (min)	Bile concn (μg/ml)
1	75	80
2	45	22
3	30	25
4	60	2.2
5	65	6.8
Mean ± standard deviation		27.2 ± 31.1

cillin, serum bilirubin, alkaline phosphatase, or creatinine.

DISCUSSION

Previous pharmacokinetic studies of piperacillin (3; J. A. Giron, B. R. Meyers, and S. Z. Hirschman, submitted for publication) have suggested a nonrenal pathway of elimination. In this study, we found very high levels of piperacillin in common duct bile 35 to 90 min after the infusion of 1 g of piperacillin; gallbladder bile levels of piperacillin were lower. No correlation with peak serum levels of piperacillin was found. Since no quantitation of bile volume was done, we could not calculate the amount of antibiotic excreted.

We speculate that biliary excretion plays a significant role in the elimination of piperacillin. Our data indicate that piperacillin is excreted in active form in bile. Piperacillin may require dosage adjustment when given to patients with hepatic impairment or to patients receiving drugs known to alter hepatic function.

The high levels of piperacillin obtained in common duct bile suggest that this antibiotic may prove useful for therapy of severe biliary infections, such as ascending cholangitis. The mean level of piperacillin found in common duct bile would inhibit 70 to 100% of *Enterobacteriaceae*, 97% of *P. aeruginosa*, 100% of *Bacteroides fragilis*, 97% of *Staphylococcus aureus* (non-beta-lactamase producers), and 100% of streptococci (5, 6, 10). These high piperacillin common duct bile levels must, of course, be viewed with the knowledge that our patients had nonobstructed biliary systems. The inability of antimicrobial agents to penetrate into the obstructed biliary tree (1, 9) adds a note of caution to our results. Clinical studies will be needed to show the effectiveness of piperacillin in patients with biliary obstruction.

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