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Decreased Biliary Excretion of Piperacillin After Percutaneous Relief of Extrahepatic Obstructive Jaundice

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The biliary excretion of piperacillin has been assessed in 11 patients with obstructive jaundice due to hilar cholangiocarcinoma. After a 1-g intravenous dose administered 30 min before preliminary percutaneous transhepatic cholangiography, no drug was detected in the bile of seven patients; in four others, drug concentrations were far below the corresponding level in serum. After a period of external biliary drainage of up to 28 days, levels of antibiotic in bile after intravenous administration were only minimally increased. The results suggest that although the impairment of hepatic function may be improved by external biliary decompression when assessed by a fall in plasma bilirubin, the biliary elimination of piperacillin and related β-lactam antibiotics may remain impaired for prolonged periods.

Piperacillin, a broad-spectrum ureido-penicillin, is normally excreted in high concentrations in bile (14), with up to 20% of the administered dose being excreted by this route (10). After a 2-g intravenous dose, mean piperacillin levels of 335 μg/ml may be achieved in bile, whereas levels up to 1,793 μg/ml have been obtained 150 min after a 4-g dose.

In the presence of biliary obstruction, the excretion of cephalosporins in bile is markedly inhibited (11, 12), and this may also be true for piperacillin, an agent which is particularly valuable in the prevention and management of septic episodes occurring in patients with complex biliary diseases (1). Preoperative decompression of the obstructed biliary tract by the percutaneous insertion of a transhepatic catheter has been advocated in the management of jaundiced surgical patients (8). Significant improvement in renal and hepatic functions may be achieved during a period of decompression (9), although the ability of the liver to excrete antibiotics in normal concentrations after such a procedure has not been demonstrated (6, 7). We have therefore examined the biliary excretion of piperacillin during a period of preoperative biliary decompression in patients with obstructive jaundice to evaluate the significance of improvement in hepatic function with regard to the biliary elimination of β-lactam antibiotics.

MATERIALS AND METHODS

Eleven patients (seven male and four female) between 37 and 85 years of age (mean age, 62.1 years), with obstructive jaundice due to hilar cholangiocarcinoma and undergoing percutaneous transhepatic cholangiography (PTC), were studied. Six patients had impaired renal function (creatinine clearance, <70 ml/min per 1.73 m^2). In eight patients, a transhepatic catheter was inserted percutaneously into the obstructed biliary tract at the time of PTC for a period of external biliary drainage before definitive surgery. All patients received 1 g of piperacillin administered intravenously over a period of 3 to 5 min 30 minutes before the commencement of the procedure.

Bile was obtained at the time of entry of the cholangiogram needle into the dilated bile ducts and before the introduction of X-ray contrast medium or the insertion of the drainage catheter. For patients undergoing external biliary drainage, an additional 1-g dose of piperacillin was given 6 h later; 1 h after this second dose, bile was obtained from the proximal drainage catheter for antibiotic assay. Toward the end of the period of biliary drainage, a single 1-g intravenous dose of the antibiotic was administered, and as before, bile was collected at 1 h for antibiotic assay. Venepuncture was performed for the assay of antibiotic in serum and for liver function tests at the time of collection of all bile samples. Bile and serum samples were held at −20°C for up to 48 h from the time of collection until drug assay. Aerobic and anaerobic cultures were performed on all bile samples, and blood cultures were obtained when indicated clinically.

Piperacillin assays of bile and serum were performed by the plate diffusion assay technique with Difco Penassay seed agar and *Micrococcus luteus* NCIB 8553 as indicator. Bile and serum samples were diluted in 0.1 M phosphate buffer (pH 6.0) before the assay, which was performed in duplicate. The limit of detection of piperacillin was approximately 1 μg/ml, and the interassay coefficient of variation was 5% at 1 μg/ml and 8% at 8 μg/ml. Gross hemobilia was not observed at any time after PTC and the insertion of a drainage catheter, and no correction of assay results was made for the presence in bile of traces of blood.

RESULTS

Values for piperacillin concentration in bile and serum at the time of initial PTC, 6 h after the insertion of a biliary drainage catheter, and toward the end of a period of external biliary drainage are listed in Table 1. For comparison, plasma bilirubin concentrations estimated at the same time intervals were also tabulated.

At the time of biliary puncture, 40 to 75 min after the first intravenous dose of piperacillin, no antibiotic was detected in the bile of 7 of 11 patients. Piperacillin levels in the bile of the remaining four patients were low (1.2 to 18.0 μg/ml; mean, 7.9 μg/ml) and much lower than the corresponding serum antibiotic concentration (2.1 to 120.0 μg/ml; mean, 43.7 μg/ml). One hour after a second 1-g dose of piperacillin administered six hours after the procedure, serum antibiotic concentrations had risen in all patients (5.3 to 140.0 μg/ml;

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TABLE 1. Biliary concentrations of piperacillin at the time of cholangiography and after percutaneous biliary drainage in patients with obstructive jaundice

Case no.	PTC					PTD[a]			
	Amt of plasma bilirubin (μmol/liter)	Concn of piperacillin (μg/ml) at:				Duration of drainage (days)	Amt of plasma bilirubin (μmol/liter)	Concn of piperacillin (μg/ml) at 1 h after dose in:	
		Biliary puncture		1 h after dose 2					
		Serum	Bile	Serum	Bile			Serum	Bile
1	348	32.0	11.0	40.0	19.0	—[b]	—	—	—
2	264	42.0	18.0	49.0	11.5	—	—	—	—
3	180	33.5	1.2	84.0	9.3	—	—	—	—
4	415	120.0	1.5	140.0	2.0	2	360	180.0	8.5
5	410	102.0	ND[c]	126.0	ND	6	360	78.0	2.5
6	230	42.0	ND	50.0	ND	11	144	29.5	6.9
7	210	15.5	ND	31.0	ND	13	116	40.5	1.5
8	103	6.4	ND	8.4	5.3	14	17	14.8	6.3
9	328	82.0	ND	94.0	2.5	16	185	98.0	11.5
10	400	3.2	ND	9.7	ND	8	210	11.6	4.2
						18	207	13.7	12.7
11	210	2.1	ND	5.3	ND	28	17	11.6	7.4

[a] PTD, Percutaneous transhepatic drainage.
[b] —, Not done.
[c] ND, Not detected.

mean, 58.6 μg/ml), and the drug was detectable in the bile of 6 of 11 patients (2.0 to 19.0 μg/ml; mean, 8.3 μg/ml) although still at concentrations far below the corresponding serum level.

The duration of biliary decompression for the eight patients who underwent this additional procedure was 2 to 28 days, with a mean duration of 13.5 days. In all cases, biliary decompression was associated with a marked improvement of hepatic function as manifest by the reduction of plasma bilirubin levels. At the time of insertion of the drainage catheter, plasma bilirubin levels, measured by a fully automated diazocolorimetric technique (Technicon SMA), were in the range 103 to 415 μmol/liter, with a mean level of 288 μmol/liter (normal range, 2 to 14 μmol/liter). After a period of biliary drainage, plasma bilirubin levels had fallen to 17 to 360 μmol/liter, with a mean level of 176 μmol/liter (Table 1). Piperacillin was detectable in the bile of all eight patients 1 h after a single 1-g intravenous dose administered at the end of the drainage period. Although antibiotic concentrations in bile were still low at this time (1.5 to 12.7 μg/ml; mean concentration, 7.2 μg/ml), when compared with the corresponding concentration in serum (11.6 to 180.0 μg/ml; mean concentration, 58.2 μg/ml), there was evidence of some minimal increase in the biliary excretion of piperacillin after a period of biliary decompression. In one patient, who received a single 1-g intravenous dose of piperacillin after 8 days of drainage and again after 18 days, a similar minimal increase in biliary excretion was noted despite a reduction in the plasma bilirubin concentration of approximately 50%.

Escherichia coli was recovered from the bile of one patient, and from one other, *Streptococcus faecalis* was isolated, both organisms being sensitive in vitro to piperacillin. No patient in this series developed clinical evidence of sepsis after PTC and the insertion of a drainage catheter with piperacillin as the sole prophylactic agent.

DISCUSSION

There was marked depression of biliary excretion of piperacillin in all patients in this study. Despite periods of biliary decompression of up to 4 weeks, levels of antibiotic in bile remained far below the concentrations normally achieved in the bile of patients without biliary obstruction. In the absence of obstruction, biliary elimination of piperacillin does not occur until approximately 20 min after intravenous administration. Peak levels in bile are achieved between 150 to 210 min after administration, although at 60 min, mean values for piperacillin in bile of approximately 150 μg/ml may be anticipated after a 2-g dose (14). The administration of prophylactic antibiotics to protect against septic complications associated with PTC and the insertion of a biliary drainage catheter is normally undertaken 30 min before the commencement of the procedure and approximately 1 h before the puncture of the biliary tree. The results obtained in this study suggest that for a 1-g intravenous dose of piperacillin, levels of antibiotic in serum at the time of biliary puncture were adequate, although the concentrations achieved in bile were unlikely to confer any additional protection against infection. In some patients in this series, the concentration of piperacillin in bile marginally exceded the typical MIC for susceptible organisms. However, bile levels were uniformly low and, despite intravenous administration, no drug could be detected in the bile of 7 of 11 (64%) patients at the time of initial PTC.

β-lactam antibiotics are excreted in bile by an active hepatocyte secretory mechanism (13), although in the presence of a biliary tract obstruction, this mechanism may be severly impaired. Although it has been proposed that percutaneous insertion of an indwelling drainage catheter for preoperative relief of jaundice reduces operative morbidity and mortality by improvement of hepatic and renal function, this has remained unproven in controlled trials (9). Moreover, this route for exogenous infection may be associated with an increased incidence of septic complications (2). Despite the rapid reduction of plasma bilirubin during biliary decompression, antibiotic elimination may remain impaired for extended periods after the relief of obstruction. Dooley et al. (3) have demonstrated prolonged serum half-life and decreased biliary excretion of mezlocillin in patients with obstructive jaundice. The results of this study suggest that biliary excretion of piperacillin in patients undergoing external decompression of the obstructed biliary tract begins to recover after decompression. However, despite long periods of external biliary drainage, the biliary elimination of piperacillin was diminished for at least 2 weeks and possibly

even 28 days. There is experimental evidence that hepatocyte function may remain impaired for up to 6 weeks after the relief of biliary obstruction (5). This has been confirmed after percutaneous biliary drainage in humans with studies of the clearance of antipyrine, an indicator of hepatic oxidative metabolism (15). The results suggest, therefore, that a marked reduction in plasma bilirubin concentration, as a marker of hepatic function, does not correlate with a similar improvement in the biliary elimination of β-lactam antibiotics.

The significance of high biliary concentrations of antibiotic in surgical prophylaxis and the treatment of established sepsis of biliary origin have been questioned (4). Although antibiotics achieving high concentrations in serum as opposed to bile have been shown to offer a reduced incidence of postoperative septic complications, the combination of serum and bile antibiotic levels in excess of the MIC for common biliary tract pathogens may afford enhanced protection. Piperacillin has been proven capable of reducing the incidence of septic complications in high-risk patients with obstructive jaundice (1). The findings of the present study suggest, however, that for patients undergoing biliary decompression as part of a staged approach to the surgical management of obstructive jaundice, excretion of this and related antibiotics may remain impaired for extended periods, although the clinical significance of this phenomenon remains uncertain.

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