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Biliary Excretion of Ciprofloxacin and Piperacillin in the Obstructed Biliary Tract

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Biliary excretion of ciprofloxacin and piperacillin was determined in cholestatic patients who had undergone endoscopic cholangiography. The median concentration of ciprofloxacin ($n = 9$) was 2.36 μg/ml (range, 0.29 to 19.8 μg/ml) in bile compared with 1.66 μg/ml (range, 0.73 to 2.69 μg/ml) in serum. The median concentration of piperacillin ($n = 7$) was <5 μg/ml (range, <5 to 26) in bile compared with 14.3 μg/ml (range, 5.3 to 80) in serum. Ciprofloxacin, but not piperacillin, can be actively excreted into bile in the presence of a biliary tract obstruction.

In the absence of a biliary tract obstruction, many antibiotics are excreted into bile, where they may reach therapeutic concentrations. In patients with a major biliary tract obstruction, however, the excretion of these same antibiotics is virtually nil (12, 13, 25). Ciprofloxacin has been claimed to reach therapeutic levels in bile despite the presence of a biliary tract obstruction (1, 13).

In this study we assessed the biliary excretion of ciprofloxacin in patients with a clinical diagnosis of biliary tract obstruction. These findings are compared with the excretion of piperacillin, a β-lactam antibiotic which is well excreted in unobstructed bile ducts but not in an obstructed biliary system (3, 24).

Patients who had undergone endoscopic retrograde cholangiography (ERCP) for obstructive jaundice due to a distal common bile duct stricture or for exchange of an obstructed biliary endoprosthesis were eligible for this study. Exclusion criteria were the use of antimicrobial drugs less than 48 h prior to ERCP or a known allergy to either penicillin or fluoroquinolones. The study was approved by the hospital ethics committee, and all participating patients gave informed consent.

Patients received either a single 500-mg oral dose of ciprofloxacin 3 h before the anticipated start of the endoscopic procedure or 4 g of piperacillin intravenously 2 h before the procedure. The time of administration of ciprofloxacin and piperacillin was chosen to make bile sampling coincide with peak concentrations of antibiotic in unobstructed bile ducts (23, 24). No randomization between the two groups took place. During ERCP a bile sample (10 to 20 ml) and a venous blood sample (7.5 ml) were taken simultaneously for determination of ciprofloxacin or piperacillin concentrations. Bile was aspirated from the common bile duct prior to the injection of contrast material. Serum was separated within 30 min of drawing the blood sample. Both bile and serum specimens were stored at −70°C until further processing.

Ciprofloxacin concentrations in serum and bile were assayed with a high-pressure liquid chromatography (HPLC) procedure (11). Precipitation of proteins was achieved by treatment of the specimens with acetonitrile and trichloracetic acid. The supernatants of the treated specimens were subjected to chromatography on a polystyrene-divinylbenzene reverse-phase column. The lower detection limit for ciprofloxacin was 0.05 μg/ml.

Piperacillin concentrations were determined by HPLC with UV detection. Identification of the drug was based on comparison of the relative retention times of an internal standard (penicillin V) and the peak of interest between the calibrating standards and controls with the appearance of peaks in the patients' samples. Piperacillin concentrations in bile and serum were determined by using the ratio of the internal standard to the piperacillin response in the patients' specimens, which is related to this ratio in the standard.

Sixteen patients were included; nine received ciprofloxacin and seven received piperacillin (Table 1). No patient in the ciprofloxacin group and one in the piperacillin group had undergone cholecystectomy in the past. Six patients in each group were clinically jaundiced. The median duration of jaundice was 6.5 days for both groups (range, 4 to 15 days).

For the ciprofloxacin group, the median interval between administration of the antibiotic and collection of the bile and blood samples was 255 min (range, 210 to 400 min). The median concentration of ciprofloxacin was 2.36 μg/ml (range, 0.29 to 19.8 μg/ml) in bile compared with 1.66 μg/ml (range, 0.73 to 2.69) in serum (Fig. 1). The bile-to-serum ratio of the ciprofloxacin concentration ranged from 0.17 to 8.87 and was greater than one in five of the nine patients.

For the piperacillin group, the median time from the administration of the antibiotic to the collection of the bile and blood samples was 142 min (range, 70 to 250 min). The median concentration of piperacillin in serum was 14.3 μg/ml (range, 5.3 to 80 μg/ml) (Fig. 2). In four patients the concentration of piperacillin in bile was below the 5-μg/ml detection level (median, <5 μg/ml; range, <5 to 26 μg/ml). The bile-to-serum ratios of the piperacillin concentration in the three patients in whom the bile concentration was above the detection level were 0.08, 0.23, and 1.04. All patients in whom the concentration of piperacillin in bile was below the detection level had serum concentrations greater than 5 μg/ml. Therefore, the

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TABLE 1. Baseline characteristics of patients before ERCP

Characteristic	Ciprofloxacin (n = 9)	Piperacillin (n = 7)	P^b
Median age (range) [yr]	72 (56–91)	64 (22–91)	
No. of patients (male/female)	6/3	5/2	
Indication for ERCP (no. of patients)			
Placement of endoprosthesis	6	5	
Exchange of endoprosthesis	3	2	
Laboratory pre-ERCP[a]:			
Total bilirubin (μmol/liter)	223 (37–438)	144 (11–316)	0.31
Alkaline phosphatase (U/liter)	632 (221–1219)	379 (179–837)	0.08
Gamma glutamyl transpeptidase (U/liter)	820 (52–1972)	353 (64–642)	0.10

[a] Median values (ranges) are given. Normal values are as follows: total bilirubin, <17 μmol/liter; alkaline phosphatase, <80 U/liter; gamma glutamyl transpeptidase, <50 U/liter.
[b] P values were calculated with the Mann-Whitney rank sum test.

bile-to-serum ratio was more than one in only one patient given piperacillin.

No correlation was evident between the biliary level of the antibiotic and the time interval between the administration of the antibiotic and the collection of the bile specimen (Spearman's rank correlation coefficient, 0.20 and 0.04 for ciprofloxacin and piperacillin, respectively).

In this study we found that ciprofloxacin, but not piperacillin, may be actively excreted into bile in the presence of a biliary tract obstruction. This is a unique property that has not been reported for any other antibiotic. Both ciprofloxacin and piperacillin are actively excreted in unobstructed bile ducts and reach bile-to-serum ratios of 25 to >50 (4, 6, 19, 21). Piperacillin excretion in obstructed bile ducts, however, is greatly diminished (3, 17). Blenkharn et al. found that even at 28 days after relief of the obstruction, the biliary excretion of piperacillin was still impaired (3). This finding suggests damage to the active mechanism by which piperacillin is excreted in patients with a biliary obstruction. This phenomenon of slow recovery after a period of obstruction was also found for other antibiotics actively excreted into bile, such as cefoperazone, cefamandole, and aztreonam (12, 14, 15).

Both ciprofloxacin and piperacillin are organic anions. The hepatic excretion of a large array of organic anions (including ceftriaxon and ampicillin) is mediated by a canalicular multispecific organic anion transporter (cMOAT) (18). There is some evidence that the excretion of fluoroquinolones (norfloxacin) also takes place via an organic anion transporter (5). Piperacillin is excreted into bile via a transport system different from the bile acid transport system, possibly cMOAT (4). The activity of cMOAT is markedly inhibited in the presence of a biliary tract obstruction and recovers slowly after restoration of bile flow (10). The impaired function of cMOAT could explain the lack of piperacillin excretion in the obstructed biliary tract but does not explain the presence of ciprofloxacin. In order to offer an explanation, we have to assume a degree of similarity between biliary and intestinal epithelia. We hypothesize that ciprofloxacin can be excreted into bile by biliary epithelial cells. Both in vitro and in vivo experiments have shown that ciprofloxacin can be actively excreted into the gut by the intestinal epithelium (7, 8, 20, 22). The exact mechanism of this excretory pathway has not been fully elucidated but appears to be independent of organic anion transporters, P glycoprotein, or intracellular Ca^{2+} and the state of calcium channels (5, 7). In the presence of a biliary tract obstruction, excretion of ciprofloxacin via cMOAT would be impaired, but excretion via the biliary epithelium apparently is not. This hypothesis would also ex-

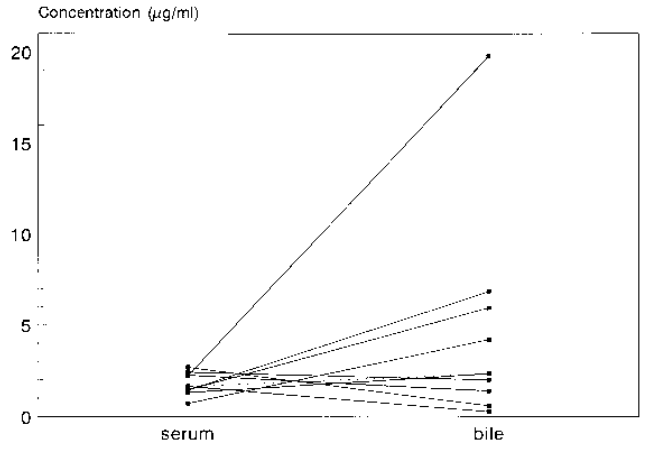

FIG. 1. Ciprofloxacin concentrations in simultaneously collected serum and bile specimens (n = 9). The dotted line connects the median values.

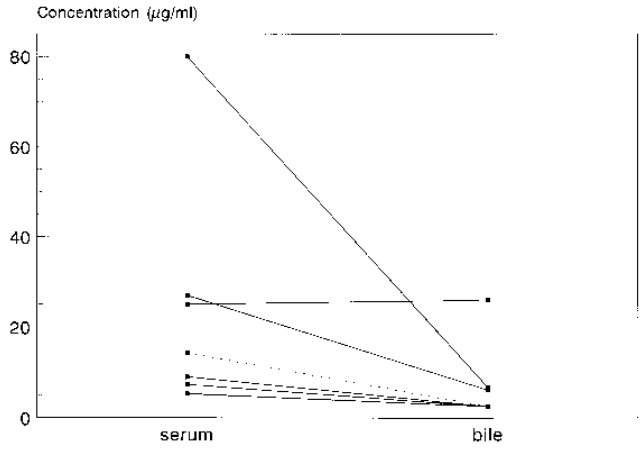

FIG. 2. Piperacillin concentrations in simultaneously collected serum and bile specimens (n = 7). For concentrations below the 5-μg/ml detection level, the concentration is arbitrarily set at 2.5 μg/ml. The dotted line connects the median values.

plain the finding that ciprofloxacin is excreted into the gallbladder after ligation of the cystic duct (9).

In this study a single dose of ciprofloxacin was given orally. Therefore, the biliary concentration of ciprofloxacin depended on the degree of absorption of the drug from the gut, as well as on biliary excretion. Serum concentrations of ciprofloxacin varied only moderately, with a factor of 3.7 between the highest and the lowest value, and were comparable to those reported previously (2, 16, 23). Hence, there is no indication that absorption from the gut is inhibited in patients with a biliary tract obstruction.

In conclusion, ciprofloxacin, contrary to piperacillin, can be actively excreted into bile and reach therapeutic concentrations in the presence of a biliary tract obstruction. We hypothesize that this is due to active excretion of ciprofloxacin by biliary epithelial cells.

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REFERENCES

1. **Ball, C. S., J. M. Manson, F. Reid, and D. E. F. Tweedle.** 1989. The pharmacokinetics of the biliary excretion of ciprofloxacin. HPB Surg. **1:**319–327.
2. **Bergan, T., S. B. Thorsteinsson, R. Solberg, L. Bjornskau, I. M. Kolstad, and S. Johnsen.** 1987. Pharmacokinetics of ciprofloxacin: intravenuos and increasing oral doses. Am. J. Med. **82**(Suppl. 4A)**:**97–102.
3. **Blenkharn, J. I., N. Habib, D. Mok, L. John, G. A. D. McPherson, R. N. Gibson, L. H. Blumgart, and I. S. Benjamin.** 1985. Decreased biliary excretion of piperacillin after percutaneous relief of extrahepatic obstructive jaundice. Antimicrob. Agents Chemother. **28:**778–780.
4. **Calhoun, P., K. B. Brown, R. Strunk, D. A. Krusch, W. M. Scheld, and J. B. Hanks.** 1987. Experimental studies of biliary excretion of piperacillin. Ann. Surg. **205:**420–427.
5. **Cao, C. X., S. C. Silverstein, H. C. Neu, and T. H. Steinberg.** 1992. J774 macrophages secrete antibiotics via organic anion transporters. J. Infect. Dis. **165:**322–328.
6. **Dan, M., N. Verbin, A. Gorea, H. Nagar, and S. A. Berger.** 1987. Concentrations of ciprofloxacin in human liver, gallbladder, and bile after oral administration. Eur. J. Clin. Pharmacol. **32:**217–218.
7. **Griffiths, N. M., B. H. Hirst, and N. L. Simmons.** 1993. Active secretion of the fluoroquinolone ciprofloxacin by human intestinal epithelial Caco-2 cell layers. Br. J. Pharmacol. **108:**575–576.
8. **Griffiths, N. M., B. H. Hirst, and N. L. Simmons.** 1994. Active intestinal secretion of the fluoroquinolone antibacterials ciprofloxacin, norfloxacin and pefloxacin; a common secretory pathway? J. Pharmacol. Exp. Ther. **269:**496–502.
9. **Grözinger, K. H., D. Beermann, H. Scholl, and F. Haaf.** 1991. Tubular transport of ciprofloxacin into the gallbladder. Eur. J. Clin. Microbiol. Infect. Dis. **10:**372–373. (Abstract.)
10. **Kothe, M. J. C., C. T. M. Bakker, J. de Haan, A. Maas, P. L. M. Jansen, and R. P. J. Oude Elferink.** 1993. Canalicular organic anion transport after bile duct ligation and reconstruction in the rat. Hepatology **18:**138A. (Abstract.)
11. **Krol, G. J., G. W. Beck, and T. Benham.** 1996. HPLC analysis of ciprofloxacin and ciprofloxacin metabolites in body fluids. J. Pharma. Biomed. Anal. **14:**181–190.
12. **Leung, J. W. C., R. C. Y. Chan, S. W. Cheung, J. Y. Sung, S. C. S. Chung, and G. L. French.** 1990. The effect of obstruction on the biliary excretion of cefoperazone and ceftazidime. J. Antimicrob. Chemother. **25:**399–406.
13. **Leung, J. W. C., T. K. W. Ling, R. C. Y. Chan, S. W. Cheung, C. W. Lai, J. J. Y. Sung, S. C. S. Chung, and A. F. B. Cheng.** 1994. Antibiotics, biliary sepsis, and bile duct stones. Gastrointest. Endosc. **40:**716–721.
14. **Levi, J. U., O. V. Martinez, T. I. Malinin, R. Zeppa, A. Livingstone, D. Hutson, and P. Calhoun.** 1984. Decreased biliary excretion of cefamandole after percutaneous biliary decompression in patients with total common bile duct obstruction. Antimicrob. Agents Chemother. **26:**944–946.
15. **Martinez, O. V., J. U. Levi, and R. G. Devlin.** 1984. Biliary excretion of aztreonam in patients with biliary tract disease. Antimicrob. Agents Chemother. **25:**358–361.
16. **Morran, C., C. McArdle, L. Petitt, D. Sleigh, C. Gemell, M. Hichens, D. Felmingham, and G. Tillotson.** 1989. Pharmacokinetics of orally administered ciprofloxacin in abdominal surgery. Am. J. Med. **87**(Suppl 5A)**:**86S–88S.
17. **Morris, D. L., Z. J. Mojaddedi, D. W. Burdon, and M. R. B. Keighley.** 1983. Clinical and microbiological evaluation of piperacillin in elective biliary surgery. J. Hosp. Infect. **4:**159–164.
18. **Oude Elferink, R. P. J., and P. L. M. Jansen.** 1994. The role of the canalicular multispecific organic anion transporter in the disposal of endo- and xenobiotics. Pharmacol. Ther. **64:**77–97.
19. **Parry, M. F., D. A. Smego, and M. A. Digiovanni.** 1988. Hepatobiliary kinetics and excretion of ciprofloxacin. Antimicrob. Agents Chemother. **32:** 982–985.
20. **Rubinstein, E., L. St. Julien, J. Ramon, S. Dautrey, R. Farinotti, J.-F. Huneau, and C. Carbon.** 1994. The intestinal elimination of ciprofloxacin in the rat. J. Infect. Dis. **169:**218–221.
21. **Russo, J., Jr., M. I. B. Thompson, M. E. Russo, B. A. Saxon, J. M. Matsen, F. G. Moody, and L. F. Rikkers.** 1982. Piperacillin distribution into bile, gallbladder wall, abdominal skeletal muscle, and adipose tissue in surgical patients. Antimicrob. Agents Chemother. **22:**488–492.
22. **Sörgel, F., K. G. Naber, U. Jaehde, A. Reiter, R. Seelman, and G. Sigl.** 1989. Gastrointestinal secretion of ciprofloxacin. Am. J. Med. **87**(Suppl. 5A)**:**62S–65S.
23. **Tanimura, H., S. Tominaga, F. Rai, and H. Matsumoto.** 1986. Transfer of ciprofloxacin to bile and determination of biliary metabolites in humans. Arzneim. Forsch./Drug Res. **36:**1417–1420.
24. **Taylor, E. W., V. Poxon, J. Alexander-Williams, and D. Jackson.** 1983. Biliary excretion of piperacillin. J. Int. Med. Res. **11:**28–31.
25. **van Delden, O. M., D. J. van Leeuwen, P. L. M. Jansen, F. J. Hoek, K. Huibregtse, and G. N. J. Tytgat.** 1994. Biliary excretion of ceftriaxon in non-stagnant and stagnant bile. J. Antimicrob. Chemother. **33:**193–194.