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Hepatobiliary Kinetics and Excretion of Ciprofloxacin

MICHAEL F. PARRY,[1,2]* DOUGLAS A. SMEGO,[2,3] AND MARIA A. DIGIOVANNI[2]

*Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York 10032[1]; Department of Surgery, New York Medical College, Valhalla, New York 10595[3]; and Stamford Hospital, Stamford, Connecticut 06904[2]**

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The biliary excretion and metabolism of ciprofloxacin was studied in 25 hospitalized patients: 19 undergoing routine cholecystectomy and 6 with indwelling biliary drainage catheters. An intravenous dose of 200 mg of ciprofloxacin given 2.5 to 3.0 h prior to cholecystectomy resulted in concentrations in common duct bile, gallbladder bile, and gallbladder wall of 5.69 ± 4.8, 5.43 ± 3.34, and 2.52 ± 1.30 μg/g, respectively, all at least fourfold greater than simultaneous concentrations in serum. Ciprofloxacin concentrations in common duct bile exceeded peak concentrations in serum in all but two patients with common duct obstruction. Multiple preoperative doses of ciprofloxacin prior to cholecystectomy increased concentrations in gallbladder bile by eightfold. Six patients with indwelling biliary drainage catheters also received 200 mg of ciprofloxacin intravenously. Less than 1% of the administered dose was excreted in bile as unchanged ciprofloxacin, and there was extensive metabolism. However, peak ciprofloxacin concentrations of 2.83 ± 0.76 μg/ml in serum produced peak concentrations of 10.69 ± 5.30 μg/ml in bile within 1.5 h after infusion and maintained concentrations of at least 0.5 μg/ml in common duct bile for over 12 h in all patients. It appears that ciprofloxacin concentrations in bile will exceed the MICs for most susceptible biliary pathogens for a period of at least 12 h after a 200-mg intravenous dose.

Biliary infections are an important source of surgical and infectious disease referral because of their propensity for causing bacteremia. Most bacteremic biliary infections are caused by enteric gram-negative bacilli, although in patients with indwelling common duct or cholecystostomy tubes and in those with biliary obstruction, nonfermenting gram-negative bacilli, anaerobes, and streptococci may be pathogenic (1, 4, 15, 17). Antimicrobial therapy for such biliary infections is traditionally selected from those compounds preferentially excreted in bile. However, adequate concentrations in blood and tissue are more important than levels found in bile for the achievement of clinical success (9). Since the quinolones possess excellent in vitro activity against the majority of biliary pathogens, we evaluated the pharmacokinetics and biliary excretion of ciprofloxacin in a group of hospitalized patients with underlying biliary disease.

MATERIALS AND METHODS

Intravenous ciprofloxacin was administered to 25 hospitalized adult patients to evaluate its pharmacokinetics. Patients were hospitalized at The Stamford Hospital or St. Joseph Medical Center in Stamford, Conn., from April 1986 to February 1987. Subjects were divided into three treatment groups. Patients in group 1, 13 patients undergoing elective cholecystectomy, received a single dose of 200 mg of ciprofloxacin (supplied by Miles Pharmaceuticals, West Haven, Conn.) intravenously for 30 min, starting 2 h preoperatively. Patients in group 2, six patients also undergoing elective cholecystectomy, received oral ciprofloxacin for 2 days in doses of 500 mg every 12 h, followed by 200 mg intravenously for 30 min starting 2 h preoperatively. Patients in group 3, six patients with indwelling biliary drainage tubes (T-tubes, four patients; percutaneous common bile duct drain, one patient; nasobiliary drain, one patient), received 200 mg of ciprofloxacin intravenously for 30 min to determine the biliary and urinary excretion patterns of ciprofloxacin. Appropriately, informed written consent was obtained from each patient prior to participation in the study.

All study patients were over 18 years of age and had normal renal function (serum creatinine values, <1.4 mg/dl). Patients with severe hepatic dysfunction, possible pregnancy, or a history of allergy to nalidixic acid or quinolone derivatives were excluded from the study. Pre- and posttreatment laboratory studies included a complete blood count, liver chemistries, serum electrolytes, and urinalysis. Twenty-four-hour urine collections for creatinine clearance were obtained from group 3 patients. Bile samples for culture were obtained from all patients. Microorganisms were identified and susceptibility studies were performed as described elsewhere by using a microbroth dilution method (14). All patients were reevaluated at 24 h and at 7 days after completion of the study for any adverse clinical or laboratory reaction. Whenever possible, the administration of additional antimicrobial agents or other pharmaceutical agents was avoided.

Blood for ciprofloxacin assay in groups 1 and 2 (cholecystectomy patients) was obtained just prior to infusion (trough), at the end of infusion (peak), and intraoperatively (time recorded). Gallbladder bile, gallbladder wall, and common duct bile samples were obtained from these patients simultaneously with the intraoperative blood sample. From group 3 patients (with indwelling common duct catheters), blood samples were obtained just prior to infusion, at the end of infusion (30 min), at 60 and 90 min, and at 2, 4, 8, and 24 h after infusion. Bile samples were obtained before infusion, and then samples were removed and volumes were measured for 0 to 30, 30 to 60, 60 to 90, and 90 to 120 min and for 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h after infusion. Concentrations in urine and volumes were determined for group 3 patients 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h after infusion. Serum was separated within 1 h of blood collection and frozen at −70°C in tightly capped polyethylene containers until assayed. Bile, urine, and tissue samples

* Corresponding author.

TABLE 1. Ciprofloxacin concentrations at cholecystectomy[a] following preoperative administration of single[b] or multiple[c] doses

Tissue or fluid assayed	Ciprofloxacin concn (μg/ml) after:	
	Single dose	Multiple doses
Predose serum		0.79 ± 0.51
Predose (peak) serum	1.59 ± 0.59	2.47 ± 0.83
Intraoperative serum	0.54 ± 0.16	1.05 ± 0.62
Common duct bile	5.69 ± 4.80	8.11 ± 4.40
Gallbladder bile	5.43 ± 3.34	44.7 ± 26.7
Gallbladder wall	2.52 ± 1.30	5.08 ± 2.76

[a] Intraoperative specimens were obtained 2.81 ± 1.23 h after administration of intravenous ciprofloxacin.
[b] Single dose, 200 mg intravenously.
[c] Multiple dose, 500 mg orally twice daily four times, followed by 200 mg intravenously.

were similarly stored. Gallbladder tissue samples were rinsed several times in sterile saline prior to freezing.

Ciprofloxacin and its metabolites, desethylene-ciprofloxacin (M1), sulfociprofloxacin (M2), and oxociprofloxacin (M3), were assayed in serum, bile, urine, and tissue by high-pressure liquid chromatography methods previously described (10). Assays were performed after sample dilution with 0.05 M potassium phosphate buffer at pH 3.0. Tissue samples were weighed and homogenized in appropriate volumes of phosphate buffer to permit calculation of micrograms of drug per gram of tissue. Bile and urine samples were chromatographed on a polystyrene-divinylbenzene column which was monitored by UV absorbance. Serum and tissue samples were chromatographed on an octadecylsilane reverse-phase column with two different chromatographic solvents. Ciprofloxacin and its M1 metabolite were measured spectofluorometrically since they have native fluorescence. Metabolites M2 and M3 were measured separately by using a photothermal postcolumn reactor. Quantitations of ciprofloxacin and each metabolite were based on peak height ratios and linear regression curves calculated from values obtained by using known concentration internal standards. Assays were highly specific and demonstrated no interference between ciprofloxacin or any of its three metabolites. Measurements were reproducible, with coefficient of variance values below 5% (10).

RESULTS

Twenty-five patients were enrolled in the study; 15 were female and 10 were male. Their mean age was 51.8 years (range, 23 to 86 years), and their mean weight was 76.0 kg (range, 50 to 98 kg). All patients had intrinsic biliary disease; 18 had cholelithiasis or choledocholithiasis, 3 had acute acalculus cholecystitis, 3 had pancreatic or cholangiocarcinoma, and 1 had sclerosing cholangitis.

In 13 patients undergoing cholecystectomy, concentrations of ciprofloxacin in common duct bile and gallbladder bile were 5.69 ± 4.8 and 5.43 ± 3.34 μg/ml, respectively, obtained an average of 2.81 ± 1.23 h after intravenous infusion of 200 mg of ciprofloxacin (Table 1). Two patients with bilirubin values of 7.1 and 17.0 mg/dl had common duct and gallbladder bile values between 0.33 and 0.68 μg/ml. Patients with normal bilirubin values achieved concentrations of 1.95 to 10.9 μg/ml in gallbladder bile and concentrations of 3.0 to 16.7 μg/ml in common duct bile. Bilirubin values in serum had no influence on peak or intraoperative levels in serum or concentrations in gallbladder wall.

Ciprofloxacin metabolites in serum measured less than 20% of simultaneous ciprofloxacin concentrations. In contrast, the total concentration of ciprofloxacin metabolites in common duct bile or gallbladder bile samples exceeded ciprofloxacin concentrations by fourfold. Total metabolites were 21.0 μg/ml in common duct bile and 23.3 μg/ml in gallbladder bile. Of the metabolites in bile, 83% was sulfociprofloxacin (M2), 13% was oxociprofloxacin (M3), and 2% was desethylene-ciprofloxacin (M1).

TABLE 2. Concentrations of ciprofloxacin in body fluids following a 200-mg intravenous dose for six patients with indwelling biliary catheters

Time after dose (h)	Ciprofloxacin concn (μg/ml) in:		
	Serum	Bile	Urine
0.5	2.55 ± 0.95	3.34 ± 2.79	
1.0	1.34 ± 0.44	7.53 ± 5.44	
1.5	1.04 ± 0.38	8.02 ± 4.55	
2.0	0.84 ± 0.41	5.46 ± 1.76	387 ± 434
4.0	0.54 ± 0.37	3.16 ± 0.72	208 ± 197
8.0	0.32 ± 0.31	1.10 ± 0.27	102 ± 66
12.0	0.21 ± 0.26	0.67 ± 0.18	52 ± 31
24.0	0.10 ± 0.16	0.28 ± 0.29	20 ± 19

Multiple oral doses of ciprofloxacin given for 48 h preoperatively, followed by 200 mg given intravenously prior to cholecystectomy, resulted in only slightly higher concentrations in serum, common duct bile, and gallbladder wall than those seen with single-dose therapy (Table 1). However, concentrations of ciprofloxacin in gallbladder bile were increased almost 10-fold by multiple-dose treatment. All patients receiving multiple doses of ciprofloxacin had normal bilirubin values, and all had serum glutamic oxalacetic transaminase values of less than 100 IU/ml.

Concentrations of ciprofloxacin in the body fluids of six patients with indwelling common bile duct catheters are summarized in Table 2 and Fig. 1. Mean peak concentrations in bile were 9.45 ± 5.64 μg/ml (range, 3.20 to 17.5 μg/ml). Patients with elevated bilirubin values had both lower and delayed peak ciprofloxacin values in common duct bile. Common duct bile concentrations of ciprofloxacin in patients with bilirubin values of >4 mg/dl (two patients) peaked at 1.5 to 2 h after infusion, compared with concentrations in patients with values of <2 mg/dl (two patients), which peaked at 0.5 to 1 h. There was a moderate correlation ($r = -0.69$) between bilirubin concentration in serum and peak ciprofloxacin concentration in common duct bile but no relationship between the serum glutamic oxalacetic transaminase value and ciprofloxacin concentration. Neither bilirubin concentration nor serum glutamic oxalacetic transaminase value bore a relationship to the concentration of ciprofloxacin in serum. In these six patients, the calculated half-life of ciprofloxacin in serum was 4.4 ± 1.5 h and the calculated half-life in bile was 3.4 ± 1.1 h.

The 24-h urinary recovery of unmetabolized ciprofloxacin from six patients with indwelling common bile duct catheters was 88.64 mg, or 44.32% of the administered dose. Total 24-h biliary recovery was 0.81 mg, or 0.41% of the administered dose.

Ciprofloxacin was administered via 21-gauge polyethylene intravenous catheters for 30 to 60 min. No phlebitis, edema, or skin irritation was noted in any subject. No other laboratory or clinical adverse reactions were seen.

DISCUSSION

The choice of antimicrobial agents for the treatment of biliary infections remains controversial. Many agents have

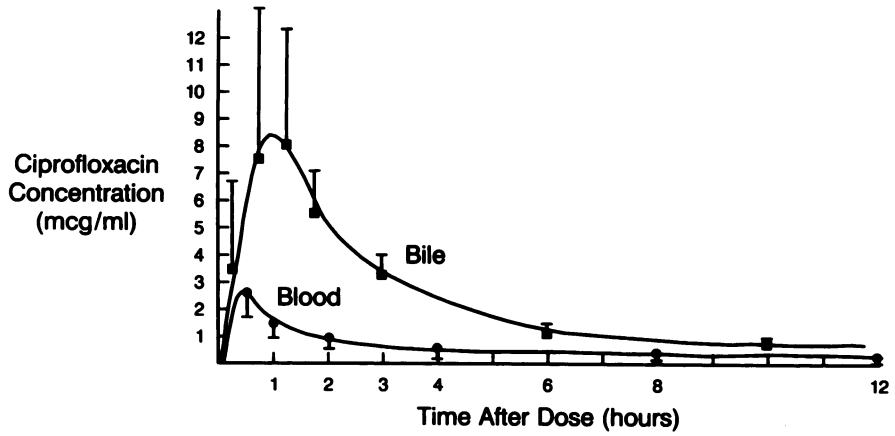

FIG. 1. Ciprofloxacin clearance. Concentrations of ciprofloxacin in blood and bile following a 200-mg intravenous dose are shown for six patients with indwelling biliary catheters.

proven useful, but the drugs of choice must all be active against aerobic gram-negative bacilli. The roles of anaerobic bacteria and enterococci are controversial. Selection of a drug which penetrates the bile in sufficient quantities to inhibit these pathogens is preferred, although its necessity is poorly documented. It appears that ciprofloxacin can be added to the list of antimicrobial agents which achieve therapeutic levels in bile in the presence of a patent or only partially obstructed biliary tree.

Despite the fact that less than 1% of intravenously administered ciprofloxacin was excreted in the bile, ciprofloxacin concentrations in both gallbladder and common duct bile were 10-fold higher than simultaneous concentrations in serum and 3-fold higher than peak concentrations in serum. Levels in common duct bile failed to equal peak levels in serum in only two patients, both of whom had common duct obstruction (bilirubin levels of 7.1 and 17.0 mg/dl). Even here, however, concentrations in bile readily exceeded the MIC of ciprofloxacin for 90% of the members of the family *Enterobacteriaceae*, commonly agreed to be 0.1 μg/ml (2, 14, 16). Multiple preoperative doses of ciprofloxacin produced an eightfold increase in concentrations in gallbladder bile compared with single-dose therapy, but only modest increases in concentrations in serum, common duct bile, and gallbladder wall (Table 1). Concentrations in tissue (gallbladder wall) were 1.7 to 2 times peak concentrations in serum.

In patients with indwelling T-tubes, all of whom had some liver dysfunction (four of six had bilirubin values of >2 mg/dl), concentrations of ciprofloxacin in common duct bile remained above the MICs for most susceptible pathogens for 24 h after a single 200-mg dose. Mean concentrations in bile 12 to 24 h after infusion were 0.28 μg/ml. Even with staphylococci and *Pseudomonas* species, for 90% of which the MICs range from 0.25 to 0.5 μg/ml (2, 14, 16), concentrations of ciprofloxacin in bile would be therapeutic for at least 12 h.

Ciprofloxacin was shown to be metabolized in the liver. Indeed, the concentrations of ciprofloxacin metabolites in common duct or gallbladder bile exceeded 20 μg/ml, four times the level of ciprofloxacin itself. Of the metabolites, 90% was sulfociprofloxacin. This compound has been shown to be the principal fecal metabolite in other studies, in which approximately 5% of an intravenous dose was recovered in the feces as sulfociprofloxacin (3). The metabolites possess some antimicrobial activity and may account for the discrepancies previously noted between high-pressure liquid chromatography and bioassay (5). However, their relative activity is less than 5% that of ciprofloxacin, so their presence should add only modestly to antimicrobial activity in bile.

Concentrations of sulfociprofloxacin and the other metabolites in feces can be accounted for chiefly by hepatic metabolism and biliary excretion. The high concentrations of unmetabolized ciprofloxacin in feces noted by other investigators (3, 5, 6), however, cannot be explained by biliary excretion alone, since only 0.4% of the administered dose was recovered in bile. Recent work by Thadepalli (H. Thadepalli, S. K. Chuah, M. D. Bansal, and A. K. Mandal, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 29, 1987) has shown that ciprofloxacin is actively secreted by the intestinal epithelium. Data from other investigators have confirmed the ability of quinolone antimicrobial agents to enter the bile and concentrate in feces. Single-dose studies of pefloxacin (12), ofloxacin (11), ciprofloxacin (5), and norfloxacin (7, 8, 13) demonstrate concentrations in bile 5 to 10 times simultaneous concentrations in serum and concentrations in feces of >200 μg/g (3, 5–7).

Ciprofloxacin concentrations in bile are appropriate for the treatment of infections due to most susceptible biliary pathogens. With multiple dosing, concentrations in gallbladder bile exceed even peak concentrations in serum 20-fold. Such levels, together with the ability of all quinolones to achieve high concentrations in feces and within phagocytic cells, may make these compounds agents of choice for the treatment of *Salmonella* carriage. Future clinical studies of other hepatobiliary infections must consider the quinolones as viable alternatives to previously used agents for the treatment of such infections in the patent or partially obstructed biliary tree.

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