ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1997, p. 1636–1640 Vol. 41, No. 8
0066-4804/97/$04.00+0

Assessment of Biliary Excretion of Piperacillin-Tazobactam in Humans

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Received 23 October 1996/Returned for modification 9 April 1997/Accepted 13 May 1997

Piperacillin-tazobactam concentrations in serum and bile were measured intraoperatively in 10 patients undergoing cholecystectomy (group 1) and 5 cholecystectomized patients provided with external bile duct drainage (group 2). Each patient received a single intravenous dose of piperacillin at 4 g plus tazobactam at 0.5 g over 30 min. Drug concentrations in both serum and bile were measured by high-performance liquid chromatography. In group 1 patients, serum and bile specimens and gallbladder wall fragments were collected at mean times of 70 and 83 min postinfusion, respectively. The mean concentrations of piperacillin and tazobactam were, respectively, 69.1 ± 41.5 (standard deviation) and 9.9 ± 5.1 μg/ml in serum, 630.4 μg/ml (range, 24.8 to 1,194 μg/ml) and 11.8 μg/ml (range, 3.6 to 22 μg/ml) in choledochal bile, 342.3 μg/ml (range, 1.1 to 1,149 μg/ml) and 7.7 μg/ml, (range, 0.2 to 23.1 μg/ml) in gallbladder bile, and 49.3 μg/g (range, 9.7 to 223 μg/g) and 2.9 μg/g (range, 0.1 to 5.9 μg/g) in the gallbladder wall. In group 2 patients, the amounts of drugs recovered in bile drainage obtained over 12 h were 28.4 ± 18.0 and 1.0 ± 0.5 mg for piperacillin and tazobactam, respectively. Peak piperacillin and tazobactam concentrations in bile reached 358 ± 242 and 10.8 ± 4.2 μg/ml, respectively. Comparison of drug levels in serum and bile suggests an underlying active secretion process for piperacillin elimination into the bile, unlike that of tazobactam. From a therapeutic viewpoint, given the concentrations of tazobactam recorded in bile fluid and tissue, the addition of this β-lactamase inhibitor to piperacillin therapy might be of interest in the management of biliary tract infections, mostly in patients at risk of mixed aerobic-anaerobic infections due to β-lactamase-producing organisms.

The factors governing the efficacies of antibiotics in biliary tract infections (BTIs) are primarily the spectrum of activity against the commonly involved pathogens in this type of infectious process, the bactericidal activity in both bile and serum, and some pharmacokinetic properties, particularly the distribution in tissues surrounding the gallbladder and the extent of biliary excretion (28).

Escherichia coli, *Klebsiella* spp., *Proteus* spp., and *Enterococcus faecalis* comprise more than 70% of the aerobic biliary pathogens involved in BTIs, with *E. coli* by far being the leading causative organism (19, 23). In addition, anaerobes, especially *Bacteroides* spp. and *Clostridia* spp., may frequently be isolated, depending on the underlying clinical condition (3, 9). Consistently, the wide variety of organisms encountered in BTIs makes the choice of an appropriate antibacterial agent somewhat awkward, and preference is usually given to a beta-lactam antibiotic that is well excreted in bile. Ureidopenicillins appear to meet relatively well the aforementioned theoretical criteria for efficacy in BTIs. In particular, mezlocillin, a ureidopenicillin highly excreted in bile, has been reported to yield great clinical efficacy in this type of infection (10).

Piperacillin-tazobactam combines a well-known ureidopenicillin and a new β-lactamase inhibitor. Piperacillin is an extended-spectrum penicillin which has been widely used in the treatment of serious infections. It is effective against most enterobacteria and also exhibits good activity against enterococci and most anaerobic bacteria. Tazobactam inhibits a wide range of commonly encountered β-lactamases of the chromosomal and plasmid-mediated types. This inhibitor appears to be more potent than sulbactam, does not induce β-lactamase production, and is usually more active than clavulanic acid against class I β-lactamases (13, 22), even though the latter activity has no clinical implications. The combination piperacillin-tazobactam provides a broader spectrum of activity than the older combinations of a β-lactam agent with a β-lactamase inhibitor (12, 15). Piperacillin-tazobactam exhibits a high level of activity against gram-positive bacteria, including strains producing β-lactamases, but not methicillin-resistant staphylococci. It is generally more potent than either of the former combinations against facultative gram-negative bacilli and obligate anaerobes (2, 15).

In a recent experimental study, we found a relatively high level of hepatobiliary excretion of piperacillin-tazobactam by using the isolated rabbit liver perfusion technique (4). The present evaluation addresses the biliary diffusion profile of this antibiotic combination in human beings and its potential role in the management of BTIs.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Hospitalo-University Center of Strasbourg. Informed written consent was obtained from each patient prior to enrollment in the study.

Patients. Fifteen patients were included in the study, and they were split into two groups. Group 1 was composed of 10 patients undergoing elective coelioscopic cholecystectomy, and group 2 included 5 patients with constant drainage of the biliary system. Antibiotics other than piperacillin-tazobactam were not administered to the patients during the study.

Patients in group 1 received preoperatively a single dose of piperacillin at 4 g plus tazobactam at 0.5 g intravenously for 30 min.

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Patients in group 2 received 4 g of piperacillin plus 0.5 g of tazobactam intravenously for 30 min to determine the biliary excretion patterns of the two drugs.

All patients studied were adults and had normal renal function, as assessed by the predictive formula for creatinine clearance of Cockroft and Gault (6). Patients with pregnancy, positive human immunodeficiency virus serology, or a history of allergy to beta-lactam antibiotics were excluded from the study. Pretreatment laboratory studies included a complete blood count, study of liver and renal chemistries, and determination of electrolyte levels.

Blood for piperacillin and tazobactam assay for group 1 patients was obtained just prior to infusion, at the end of infusion, and intraoperatively at the time that bile samples were obtained. Intraoperative specimens of serum, gallbladder bile, and choledochal bile were obtained simultaneously 1.13 ± 0.25 h after the end of the perfusion, while fragments of the gallbladder wall were sampled a few minutes later (1.37 ± 0.40 h).

Concerning group 2 patients, a 1-week lag period separated the study day from the operative day. Blood samples were obtained just prior to infusion, at the end of infusion, and at 1, 2, 3, 4, 5, 6, 8, and 12 h after infusion. Bile samples were obtained before infusion, and then the samples were removed and the volumes were measured for the intervals of 0 to 30, 30 to 60, and 60 to 120 min and 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 8, and 8 to 12 h after infusion. Urine was collected for three consecutive intervals of 0 to 6, 6 to 12, and 12 to 24 h after infusion.

Serum was separated within 1 h of blood collection and was frozen at −80°C in polypropylene containers until it was assayed. Bile, urine, and gallbladder wall samples were placed on ice upon collection and were stored as described above for blood. Gallbladder wall samples were rinsed in sterile distilled water prior to storage.

Antibiotic assays. Piperacillin and tazobactam concentrations in serum, bile, and urine were measured by high-performance liquid chromatography (HPLC) as described previously (14).

(i) Tazobactam levels in serum. For the measurement of tazobactam levels in serum, 500 μl of the sample was supplemented with 10 μl of saturated sodium monohydrogen carbonate in a screw-cap glass tube, and after mixing, the solution was deproteinized with 50 μl of trifluoroacetic acid. After mixing and centrifugation (3,000 × *g*, 10 min), the supernatant was transferred to another tube and was mixed with 1 ml of chloroform. After 15 s of vortexing and 15 min of centrifugation at 3,000 × *g*, the supernatant was kept in ice until the HPLC analysis.

For the mobile phase of the HPLC analysis of tazobactam, a solution of 80 mM phosphate buffer (pH 6.5) containing 5% acetonitrile was used. The flow rate was 1 ml/min, and separations were performed on a high-speed C_{18} reverse-phase analytical column (75 by 4.6 mm; Ultrasphere ODS; Beckman). Detection was with UV light at A_{214}. Under these conditions, the retention time of tazobactam was 2.6 min.

(ii) Piperacillin levels in serum. For piperacillin, 500 μl of serum was deproteinized with 500 μl of acetonitrile in a screw-cap glass tube. After mixing and centrifugation (3,000 × *g*, 10 min), the supernatant was transferred to another screw-cap glass tube and was mixed with 3.5 ml of methylene chloride. After mixing (10 min, 20 rpm) and centrifugation (3,000 × *g*, 10 min), the final supernatant was used for the HPLC analysis of piperacillin.

For the mobile phase, a solution of 20 mM ammonium acetate adjusted to pH 5 with acetic acid and containing 24% acetonitrile was used. The separations were performed on the same type of analytical column that was used for tazobactam, and a flow rate of 1 ml/min was used. Detection was done at 214 nm. Under these conditions, the retention time of piperacillin was 4.3 min.

(iii) Urine and bile. All urine and bile samples were centrifuged, diluted (1:20 and 1:10, respectively), and injected into the chromatograph.

(iv) Gallbladder wall samples. Gallbladder wall samples were washed rapidly with phosphate buffer (pH 7), dried, weighed, frozen at −80°C, and homogenized frozen in a Freezer Mill System under liquid nitrogen. The resulting powder was mixed in 1 ml of phosphate buffer, shaken for 4 hours at 4°C, filtered, and ultrafiltered. The ultrafiltrate was used for HPLC analysis.

For both drugs, the analytical procedures were validated by control of precision, accuracy, recovery, and limits of detection. Precision was assessed by investigating the within- and between-day reproducibilities in sera as well as in bile or urine at both low and high concentrations of each drug. The resulting data were obtained each time with 10 samples which were initially free of drugs and supplemented with amounts of drugs yielding the study concentrations; none of the calculated coefficients of variations exceeded 8%. Accuracy was always characterized by a deviation of less than 8% from the targeted values. The limits of detection of piperacillin and tazobactam were 0.05 μg/ml in serum, bile, or urine and 0.1 μg/g in gallbladder fragments.

Kinetic analysis. Pharmacokinetic parameters for piperacillin and tazobactam were determined by the usual noncompartmental methods (11). The peak concentrations in bile and the times of their appearance were obtained by visual inspection of the data. Values for the elimination rate constant (β) were estimated by linear regression of the semilogarithmic plot of the last four concentrations in serum versus time. The elimination half-lives ($t_{1/2\beta}$) were calculated from $t_{1/2\beta} = \ln 2/\beta$.

The total clearance of each drug (CL) was obtained from the equation CL = dose/$AUC_{0-\infty}$, where $AUC_{0-\infty}$ is the area under the serum concentration-time curve extrapolated to infinity by dividing the last measurable concentration by β.

TABLE 1. Piperacillin and tazobactam concentrations at cholecystectomy following preoperative administration of single intravenous doses of 4 and 0.5 g, respectively[a]

Tissue or fluid assayed	Mean concn (μg/ml or μg/g [range])[b]	
	Piperacillin	Tazobactam
Preoperative serum	254.3 (102.4–460)	29.5 (11.2–53.2)
Intraoperative serum	69.1 (26.8–143.6)	9.9 (6.0–20.1)
Common duct bile	630.4 (24.8–1194)	11.8 (3.6–22.0)
Gallbladder bile	342.3 (1.1–1149)	7.7 (0.2–23.1)
Gallbladder wall	49.3 (9.7–223)	2.9 (0.1–5.9)

[a] Preoperative serum specimens were obtained at the end of the perfusion. Intraoperative specimens were obtained 1.13 ± 0.25 h (serum and bile) and 1.37 ± 0.40 h (gallbladder wall) following the end of piperacillin-tazobactam perfusion.

[b] Values are in micrograms per milliliter for serum and bile and micrograms per gram for gallbladder wall.

Renal clearance (CL_R) and biliary clearance (CL_B) were calculated by dividing the amounts of unchanged drug excreted in the urine and in the bile, respectively, by $AUC_{0-\infty}$.

Correlations between some results of the kinetic studies were examined. Given the small number of the subjects enrolled in the study and the relatively wide range of values recorded, a nonparametric test (the Spearman's range correlation test) was used (8).

RESULTS

Patients undergoing intraoperative sampling (group 1). Of the 10 patients undergoing intraoperative sampling (group 1), 6 were female and 4 were male. Their mean age was 46.9 ± 8.6 (standard deviation [SD]) years (range, 34 to 60 years), and their mean weight was 78.6 ± 17.0 kg. All the patients had cholelithiasis without common bile duct obstruction. Regarding liver function status, there were no cases of cholestasis and only one patient presented with a moderate elevation in aminotransferase level; i.e., it was lower than twice the upper limit of the normal values.

The concentrations of piperacillin and tazobactam in intraoperative specimens are given in Table 1. The mean ratios of the piperacillin concentration in gallbladder bile/that in intraoperative serum, the piperacillin concentration in common duct bile/that in intraoperative serum, and the piperacillin concentration in the gallbladder wall/that in intraoperative serum were 5.3, 9.6, and 1.08, respectively. The corresponding ratios for tazobactam were 0.73, 1.07, and 0.35, respectively. There was a significant correlation ($r = 0.745$; $P < 0.05$) between the concentration of tazobactam in intraoperative serum samples and the simultaneous drug concentration in the gallbladder wall. Such a relationship was not found for piperacillin.

Patients provided with external biliary drainage (group 2). Of the five patients provided with external biliary drainage (group 2), four were female and one was male. Their mean age was 56 ± 12 years (range, 37 to 67 years), and their mean weight was 87.4 ± 15.3 kg. All patients had intrinsic biliary disease including choledocholithiasis. A moderate hepatic cytolysis was present the day before the study in all patients: aspartate aminotransferase range, 30 to 59 IU/liter (mean, 41 ± 11 IU/liter); alanine aminotransferase range, 50 to 191 IU/liter (mean, 86 ± 60 IU/liter).

The concentrations of piperacillin and tazobactam in the serum or bile of five patients with indwelling bile duct catheters are presented in Fig. 1. The kinetic parameters for both drugs are given in Table 2. The cumulative amount of unchanged drugs recovered in the bile drainage obtained over 12 h averaged 28.4 ± 18.0 mg for piperacillin and 1.0 ± 0.5 mg for tazobactam, i.e., 0.7% ± 0.4% and 0.2% ± 0.1% of the dose,

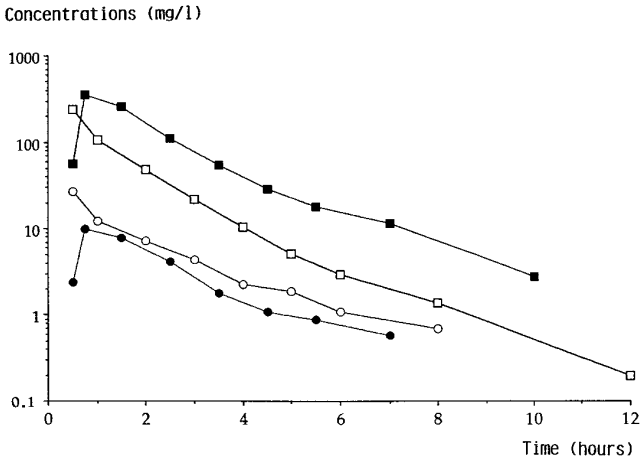

FIG. 1. Mean concentrations (in a semilogarithmic plot) of piperacillin (squares) and tazobactam (circles) in serum (open symbols) and bile (closed symbols) after administration of an intravenous dose of piperacillin at 4 g plus tazobactam at 0.5 g over 30 min in five subjects (study group 2).

respectively. CL_B varied greatly between the patients, ranging from 0.49 to 3.74 ml/min (mean, 1.74 ± 1.33 ml/min) for piperacillin and from 0.17 to 1.15 ml/min (mean, 0.46 ± 0.40 ml/min) for tazobactam.

There was no correlation between the amount of either drug recovered in the bile drainage over 12 h and the cumulative volume of bile secreted over 12 h.

Of note, a significant inverse correlation was found between the amount of piperacillin recovered in the bile drainage over 24 h and the level of aminotransferases in serum ($r = -1.0$; $P < 0.05$).

The recovery of piperacillin and tazobactam in urine over 12 h amounted to 1,700 ± 990 mg and 300 ± 135 mg, respectively, which is 42.5 and 60.0% of the corresponding administered doses.

DISCUSSION

The data on the disposition of piperacillin obtained for group 1 patients (intraoperative sampling) indicate that the amount of piperacillin in the biliary tract is much higher than that of tazobactam, with the ratio of the mean concentration of piperacillin/mean concentration of tazobactam exceeding by far the 8/1 ratio in the administered formula. Whereas our data concerning the penetration of tazobactam into the bile are unique, those for piperacillin may be compared with what we obtained previously for piperacillin given as a single agent by the same methodology (5). In intraoperatively collected choledochal bile, gallbladder bile, and gallbladder wall samples ($n = 10$ subjects), the concentrations of piperacillin simultaneously measured 1 h after the intravenous administration of a 2-g dose were 382 ± 110 μg/ml, 30.8 ± 2.5 μg/ml, and 10.5 ± 2.6 μg/g, respectively. Whereas the piperacillin dose given in the present study is twice that given in the former study, the mean drug concentrations recorded in the present evaluation appear to be approximately 10 and 5 times higher in gallbladder bile and the gallbladder wall, respectively, than the corresponding values reported previously after administration of a 2-g dose of piperacillin (5). This discrepancy is likely to be accounted for by differences in the permeability of the cystic duct. The significant correlation between tazobactam concentrations in intraoperative serum and in the gallbladder wall, combined with the lack of such a relationship for piperacillin, might mean that the antibiotic concentration in the gallbladder wall could be influenced more by the antibiotic concentration in the gallbladder bile than by the antibiotic concentration in the bloodstream when the ratio of the concentration in bile/concentration in serum is >1.

The data obtained for group 2 patients (external bile drainage) indicate that the disposition and elimination parameters of piperacillin and tazobactam (Table 2) are roughly comparable to those reported by Sorgel and Kinzig (24) and Wise et al. (30) for healthy subjects who received the same dosage.

The biliary recovery of piperacillin over 12 h is approximately 0.7% of the administered dose, which is similar to the value found in our previous study, i.e., 0.65% (5). Although comparison between different studies is hazardous, this result might indicate that the association with tazobactam would not influence the hepatobiliary elimination of piperacillin. On the other hand, it appears that hepatic impairment, characterized by cytolysis, does modify the extent of biliary excretion of piperacillin. Indeed, there is a significant inverse correlation between the degree of hepatic cytolysis and the extent of piperacillin recovery in the bile drainage over 24 h. This is in accordance with previously reported data (27, 28), indicating that the biliary excretion of antibiotics is reduced in patients with hepatic function impairment, most likely through a decrease in drug uptake into hepatocytes or a transfer from liver cells into the bile, or both.

Due to hepatic dysfunction and incomplete bile collection as a result of the use of external bile drainage by an indwelling catheter, the piperacillin-tazobactam excretion rate in bile found in this study should be viewed as an underestimate of the amounts that can be obtained. However, even if bile collections represent as little as 50% of the total flow, the average amount of both drugs excreted in bile (which would be doubled) combined with urinary elimination data account for about 50% of the administered dose. Hence, it is clear that an additional mechanism(s) for the elimination of these drugs must exist. Indeed, both piperacillin and tazobactam undergo hepatic metabolism. In a study with ^{14}C-labelled tazobactam in six healthy volunteers, an average of 26% of ^{14}C-labelled M_1 metabolite was found (24). In contrast, the two metabolites formed by β-lactam ring cleavage contribute little (<10%) to the overall elimination of piperacillin (21). Accordingly, gastrointestinal

TABLE 2. Pharmacokinetic parameters for piperacillin at 4 g and tazobactam at 0.5 g following a single intravenous injection in group 2 patients[a]

Drug	$C_{0.5}$ (μg/ml)	C_6 (μg/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2\beta}$ (h)	CL (ml/min)	CL_R (ml/min)	CL_B (ml/min)	Amt (mg) in bile from 0 to 12 h	C_{max} (mg/liter) in bile
Piperacillin	242.6 ± 90.7	3.0 ± 1.8	296.0 ± 83.9	1.14 ± 0.19	276.0 ± 128.0	96.6 ± 52.3	1.74 ± 1.33	28.4 ± 18.0	358 ± 242
Tazobactam	26.9 ± 8.5	1.1 ± 1.2	43.6 ± 16.4	1.38 ± 0.90	196.0 ± 96.0	129.0 ± 90.8	0.47 ± 0.40	1.0 ± 0.5	10.8 ± 4.2

[a] Data are means ± standard deviations for five patients. $C_{0.5}$ and C_6, concentrations in serum at 0.5 and 6 h after the end of infusion, respectively; C_{max}, maximum concentration of drug in serum. The other abbreviations are defined in the text.

secretion of piperacillin might be substantial, but as yet it has not been documented.

The high levels of piperacillin achieved in gallbladder or choledochal bile suggest that the drug undergoes active biliary secretion. Carrier-mediated transport systems appear to be important in the biliary secretion of compounds which are concentrated in bile (i.e., concentration in bile to concentration in plasma ratio, >1.0), and the transport sites may be located in the hepatic plasma membrane and/or the canalicular membrane (20).

Anionic beta-lactams have been shown to use carrier-mediated transport systems located both in the sinusoidal membrane and in the canalicular membrane of the hepatic cell (25, 26). Intrahepatic protein binding of anionic beta-lactams by ligandin is also an important factor determining the extent of biliary excretion of these drugs (16).

Given that both piperacillin and tazobactam are anionic species at physiological pH values, the difference between these drugs with regard to their respective extents of biliary excretion might be explained by the different molecular weights, i.e., 517.6 and 300.3 for piperacillin and tazobactam, respectively (24). Indeed, it has been shown that above a threshold value of 450 to 500, the biliary excretion of anionic beta-lactams in humans becomes more substantial (7), as shown recently for cefixime (29).

From a clinical viewpoint, it has been emphasized that in terms of prophylaxis, the important sites for high antibiotic concentrations are the tissues surrounding the gallbladder, the wound, and the blood to prevent the spread of organisms at the time of surgical manipulation. The levels of both piperacillin and tazobactam recorded in intraoperative samples appear to be higher than the lower breakpoint used in France to define the susceptibility of most bacteria to piperacillin, i.e., 8 μg/ml, and also higher than the concentration of 4 μg/ml found to be effective in vitro against tazobactam-susceptible β-lactamases. Piperacillin-tazobactam could thereby be useful for the prophylaxis of perioperative infection.

With regard to antibiotic therapy for acute cholangitis, the antibacterial spectrum of the combination piperacillin-tazobactam appears to be theoretically quite adequate. In terms of antibacterial activity, it has recently been shown that the pharmacodynamics of β-lactamase inhibitor–β-lactam combinations are not dependent upon maintenance of a critical ratio between the components (1, 18). In addition, it has appeared that it is the concentration of tazobactam, but not that of piperacillin, which is the important limiting factor determining the activity of the combination (17). In our study, however, tazobactam concentrations concomitantly obtained in both serum and bile exceed 4 μg/ml only during the first 3 h after dosing. Consequently, tazobactam should not restore the activity of piperacillin during the entire interval between doses (usually 6 to 8 h). Whether this drawback could significantly affect the usefulness of piperacillin-tazobactam in the management of BTIs is unclear due to the lack of data from clinical studies in this area so far. The incidence of β-lactamase-producing members of the family *Enterobacteriaceae* in BTIs is not known. The fact remains that the combination piperacillin-tazobactam could be useful for the treatment of those cases of BTI in which a mixture of aerobic and anaerobic organisms is likely to be involved, namely, cholangitis in elderly people or patients with previous bile duct-bowel anastomoses (3).

It should be remembered, however, that the treatment of BTIs relies primarily on bile duct desobstruction.

ACKNOWLEDGMENTS

We thank C. Gallion, S. Niedergang, and R. Leininger for excellent technical assistance.

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