Effects of Cirrhosis on Kinetics of Aztreonam

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Aztreonam was administered as a single, 3-min, 1-g intravenous infusion to 18 subjects, including 6 with biopsy-proven, primary biliary cirrhosis, 6 with biopsy-proven, stable alcoholic cirrhosis, and 6 age- and sex-matched control subjects with normal hepatic functions. Aztreonam was well tolerated by all subjects. Multiple blood samples and timed, cumulative urine samples were taken for assay of aztreonam content and determination of pharmacokinetic profiles. Protein-free filtrates of serum were also assayed for drug levels. Analyses by microbiological and high-pressure liquid chromatographic procedures gave equivalent results. The kinetic data were described by an open, linear, two-compartment model. There were significant differences in elimination half-life (3.2 versus 1.9 h), serum clearance (0.8 versus 1.1 ml/min per kg), and nonrenal clearance (0.2 versus 0.4 ml/min per kg) between the alcoholic cirrhosis group and the normal control group and in elimination half-life (2.2 versus 1.9 h) between the primary biliary cirrhosis group and the normal control group. There was also a difference in nonrenal clearance between the alcoholic cirrhosis and primary biliary cirrhosis groups (0.2 versus 0.5 ml/min per kg). Although the handling of aztreonam differed in the three groups, the magnitude of the difference would warrant a change in aztreonam dosing only for the alcoholic cirrhosis group. In this group, dose adjustment might be required if long-term therapy with high doses of aztreonam is indicated.

Previous studies have shown that biliary excretion plays a role in the elimination of aztreonam. In healthy male subjects given 14C-labeled aztreonam intravenously, 12.3% of the total radioactivity appeared in the feces, reflecting biliary secretion (19). In patients with biliary tract cannulation because of total obstruction of the common bile duct, biliary excretion accounted for a mean of 0.18% of the total administered dose (9). In patients with T-tube insertion postcholecystectomy, mean peak biliary concentrations of ca. 40 μg/ml were reached 2.4 h after a single 1-g dose of aztreonam (9). Animal studies have also shown that aztreonam is excreted in the feces via the biliary route (16).

The present study was undertaken to compare the pharmacokinetics and safety of aztreonam when administered as a single, intravenous infusion to patients with cirrhosis, both primary biliary (PBC) and alcoholic (AC), and in normal age-matched control subjects (NC).

MATERIALS AND METHODS

The study was conducted in the Clinical Pharmacology Unit, Rush-Presbyterian-St. Luke’s Medical Center, Chicago, Ill. Eighteen participants were entered into the study after giving written informed consent. Included were 6 subjects designated as healthy controls after screening by history evaluation, physical examination, and laboratory determinations and 12 subjects designated as cirrhotic by laboratory parameters and liver biopsy. Of the cirrhosis patients, six suffered from PBC and six suffered from AC. The cirrhosis patients were clinically stable and well compensated. Drug therapy for all participants was discontinued at least 1 week before the day of dosage with aztreonam. Patients were assigned study numbers on the basis of diagnosis and therefore were not given the drug according to numerical order. Relevant predrug laboratory parameters are listed for the 18 subjects in Table 1. Of the six patients, all female, designated as PBC, subjects 1 to 6, one patient (subject 4) presented a complicated cirrhosis pattern with probably overlying AC. She had undergone portacaval shunting 7 years before the study. Subject 2 had some features which were atypical for isolated PBC, but the remaining four subjects were classified as II to III. Three PBC patients (subjects 1, 2, and 5) had undergone cholecystectomy 2 months to 19 years before the study. In the AC group (subjects 7 to 12), all subjects were male. Subjects 8 and 11 had undergone previous cholecystectomy, whereas subject 9 had undergone portacaval shunt. All were free from ascites or edema. All subjects were screened for hepatitis B surface antigens, whereas two subjects (subjects 7 [AC] and 14 [NC]) had glucose-6-phosphate dehydrogenase deficiency. No hemolysis was detected after the administration of aztreonam.

Each participant while in fasting state received a single 1-g dose of aztreonam formulated with arginine, reconstituted in 10 ml of sterile water, as a 3-min intravenous infusion, using a Harvard infusion pump. Blood samples for aztreonam determination were obtained through an indwelling intravenous catheter before administration of the dosage and at 10, 20, and 30 min and 1, 1.5, 2, 3, 4, 6, 8, and 12 h after the termination of the drug infusion. Additional blood was obtained at the 2- and 4-h sampling time for measurement of serum protein binding by the ultrafiltration technique (15). Before the administration of aztreonam, a 0-hour urine sample was obtained, and after drug infusion, cumulative urine collections were made for aztreonam assay. The time periods for the urine collections after drug infusion were 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h. All blood samples were allowed to clot for 15 min and then were centrifuged under refrigeration for 15 min. The resultant serum specimens were transferred to polypropylene tubes, capped, and frozen at −60°C until analyzed. The additional 2- and 4-h blood samples were processed to obtain protein-free filtrate for aztreonam assay by the standard

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ultrafiltration technique (15), using Centriflo membrane cones (Amicon Corp.) (molecular weight exclusion, 50,000), in an IEC PR-6000 refrigerated centrifuge. The protein-free filtrates were then placed in polypropylene tubes, capped, and held at -60°C until analyzed.

All aztreonam assay procedures were performed by The Squibb Institute by two methods: a microbiological agar diffusion method with Escherichia coli SC 12155 as the test organism and a high-pressure liquid chromatographic assay (HPLC) (18). The two methods were undertaken to compare the accuracy of HPLC with the standard microbiological assay, as well as to determine metabolite levels. All data were analyzed at The Squibb Institute for pharmacokinetic parameters which were computed on an IBM 370 digital computer with the Autoan and Nonlin programs (11). Serum clearance was obtained from blood sample determinations, and renal clearance was calculated with the addition of urinary excretion data. Nonrenal clearance was determined by subtracting renal from total serum clearance. Statistical analyses of the data for each pharmacokinetic parameter were performed by using analysis of variance techniques. Significance tests between the three groups were done on the natural logarithm of the data by using the Duncan multiple range test.

All participants were questioned for any relevant symptoms and were evaluated by physical examination, hematological and biochemical blood determinations, urine analyses, and 12-lead electrocardiograms before and from 48 to 72 h after drug administration. Vital signs, which included temperature, heart rate, respiratory rate, and sitting blood pressure determination, were recorded before and at 0.25, 1, 2, 4, and 12 h after aztreonam infusion.

### RESULTS

No changes in clinical status, vital signs, or laboratory data were seen from predrug screening to postdrug evaluation for any subject. All subjects tolerated the drug and procedures well.

Mean aztreonam concentrations in serum, determined for each sampling time by bioassay, are given in Table 2, and mean urinary concentrations, determined by bioassay, are shown in Table 3. The percentage of aztreonam that bound to protein, calculated from measurements of aztreonam in serum and in protein-free filtrate of serum, ranged from 69.4% in the AC group to 74.4% in the NC group. No significant differences were found among groups or between the 2- and 4-h sampling times. These values correspond to those found in healthy subjects in a previous study (19).

The two methods of aztreonam assay were compared; the HPLC method gave results equivalent to those of the microbiological assay, with correlation coefficients of 0.99, 0.99, and 0.92 for serum, urine, and protein-free filtrate concentrations, respectively. The HPLC values were, on the average, 0.9 times the microbiological assay values. No detectable metabolite was found in serum or protein-free filtrate (quantitation limit of the metabolite assay was 1 μg/ml). However, ca. 1 to 2% of the dose administered was recovered in 12-h urine collections as the open-ring biotransformation product, with no significant difference among the three groups (1.90 ± 0.22% in NC, 1.45 ± 0.24% in PBC, and 1.58 ± 0.16% in AC).

Detailed pharmacokinetic analysis was performed by using total serum concentrations of aztreonam measured by bioassay, because that analytical method had lower quantitation limits than the HPLC method. Selected mean pharmacokinetic parameters by diagnostic group are presented in

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<th>Group</th>
<th>Subject no.</th>
<th>Alb</th>
<th>Creat</th>
<th>SGOT/SGPT</th>
<th>Alk phos</th>
<th>PT</th>
<th>Bili</th>
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<td>4.1</td>
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<td>16</td>
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<td>28/16</td>
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<td>37/27</td>
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<td>23/18</td>
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<td>48</td>
<td>13.0</td>
<td>1.78</td>
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*Alb = Albumin (grams per deciliter); creat, creatinine, (milligrams per deciliter); SGOT/SGPT, serum glutamic-oxalate transpeptidase (IU per liter), serum glutamic aspartate transpeptidase (IU per liter); Alk phos, alkaline phosphatase (IU per liter); PT, prothrombin time (seconds); Bili, bilirubin (milligrams per deciliter).
Table 4. The biphasic serum concentration curves indicated that aztreonam pharmacokinetics were described by an open, two-compartment kinetic model. Serum clearance of aztreonam was calculated to be 1.0, 0.8, and 1.1 ml/min per kg for the PBC, AC, and NC groups, respectively. Elimination kinetic data were derived from 12-h urinary recovery of aztreonam by the bioassay method of analysis. Renal excretion ranged from an average of 54% in PBC to 76% in AC, with NC excreting an average of 62% of dose after 12 h.

Statistically significant differences in pharmacokinetic parameters were found in the following categories: (i) serum clearance of aztreonam for AC versus the NC groups (P < 0.05); (ii) serum t1/2B of aztreonam for both PBC and AC versus the NC groups (P < 0.05); (iii) renal excretion of aztreonam for PBC versus AC groups (P < 0.05); and (iv) nonrenal clearance of aztreonam for AC versus both PBC (P < 0.01) and NC (P < 0.05) groups.

Although the number of subjects per group is small, making statistical evaluations more difficult, a definite trend is seen. The two cirrhosis groups differ from the NC group, and in addition, the two cirrhosis groups differ from one another. The terminal half-life of aztreonam is significantly higher in both groups of cirrhosis patients than it is in healthy, age- and sex-matched control subjects. The prolongation of t1/2B is more striking in the AC patients. The prolonged half-life results primarily from changes in serum clearance of the drug and not from changes in volume of distribution. The renal clearance did not differ significantly among the groups, but nonrenal clearance for AC patients differed significantly from NC subjects and from PBC patients. The PBC patients showed only modest differences from healthy subjects in nonrenal clearance and elimination half-life. Thus, there appears to be a difference between the AC group and the PBC group in terms of the handling of aztreonam.

DISCUSSION

In the PBC patients studied, four were classified as stages II to III and thus had diffuse obstruction of the biliary tree without formation of fibrous septa (7, 14). These four patients had elevated alkaline phosphatase and bilirubin levels, reflecting cholestatic lesions with preserved parenchymal function. The remaining two patients in this group showed some evidence of hepatocellular dysfunction, with slightly prolonged prothrombin times and low to low-normal albumin levels. However, data on all six patients were combined to evaluate mean data in this group. Comparison of pharmacokinetic parameters in the PBC group versus NC group showed a modest but significant prolongation of elimination half-life but comparable renal and nonrenal serum clearance of the drug.

In the AC group, synthetic function of hepatocytes (5, 12) was relatively impaired, as reflected in the prolonged prothrombin time (17) in four of the six patients. However, all of these patients were clinically stable with no evidence of edema, ascites, or decompensated liver function. This group showed a more pronounced alteration in the handling of aztreonam, with a calculated elimination half-life of 1.7 times that of the NC group. Total serum clearance was decreased, resulting from the decrease in nonrenal clearance, which was 0.5 and 0.4 times that of the NC and PBC groups, respectively.

Several antibiotics are known to be handled by the liver, either (i) through biliary excretion or enterohepatic circulation with high biliary levels (or both) but little or no metabolism or (ii) through biotransformation. Included in the
first category are such drugs as ampicillin, mezlocillin, carbenicillin (22), and certain other penicillin derivatives, including cephalothin, cefamandole, clindamycin, and erythromycin (1, 8, 10, 13). The second category of drugs handled by the liver include rifampin, chloramphenicol, and isoniazid. Liver disease is known to affect the handling of these second-category drugs, but with the exception of chloramphenicol, the change in dosing requirements in liver disease is not clear. Liver disease decreases the biliary concentrations of drugs normally concentrated in the bile, such as erythromycin, ampicillin, nafcillin, and cefamandole (1). Little data is available relating the type of liver disease to the differences in the handling of these antibiotics (3).

Ampicillin is handled similarly to drugs in the first category, with a biliary excretion component but elimination of the majority of the unchanged drug via the kidney (20). This study suggests that hepatocellular disruptions, rather than biliary tree abnormalities, are the most important factors in altering the handling of ampicillin. This difference was discernable in patients with stable, controlled disease and might be more important in patients with more severe derangement of hepatocellular function. The 20 to 25% decrease in clearance of ampicillin seen in the AC group in this study would suggest that a significant accumulation of ampicillin would occur with prolonged administration of the drug. However, the reduction in clearance of ampicillin by AC patients is less than that reported for clindamycin (21), ampicillin (22), or mezlocillin (4). With ampicillin, as with these drugs, a high therapeutic index allows for a wide range of serum levels before toxicity is manifested.

Long-term, high-dose therapy may be adjusted by a 20 to 25% reduction in dose in patients with proven stable AC when indicated clinically, but little or no adjustment is required in stable PBC patients. The effect of unstable or decompensated liver disease on ampicillin handling remains to be evaluated.

LITERATURE CITED


