Biliary Elimination of Apalcillin in Humans

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Apalcillin was administered intravenously as a single 1-g dose on day 8 after surgery to 10 cholecystectomized patients with T-tube drainage. A peak of 2,093 ± standard error of the mean 859 μg/ml of bile was attained at 3 h after dosage. Biliary recovery over a 12-h period amounted to 12.2% of the dose. In 20 patients undergoing biliary surgery, apalcillin concentrations 1 h after a 1-g dose were 65.5 ± 5.0, 3,680 ± 551, and 2,552 ± 627 μg/ml in serum, choledochal bile, and gallbladder bile, respectively.

Apalcillin (formerly PC 904) is a semisynthetic derivative of the ureido-penicillin group. Because of its high activity against most microorganisms responsible for most biliary tract infections, it appeared useful to evaluate its biliary excretion in humans. In a first group of 20 patients undergoing cholecystectomy for cholecystitis, cholelithiasis, or both, without obstruction of the common bile duct, antibiotic levels were determined in serum, choledochal bile, and gallbladder bile taken simultaneously during the operation, 1 h after intravenous administration of 1 g of apalcillin.

In a second group of 10 cholecystectomized patients with T-tube drainage, apalcillin levels in serum and bile were measured at hourly intervals for 12 h after an intravenous dose of 1 g. This study was carried out on day 8 after surgery, when the daily output of bile through the T-drain was estimated to be ca. two-thirds of total bile flow (6). This postoperative delay was intended to minimize the effect of factors (anesthesia, operative shock, administration of antibiotics and fluids) that could alter bile flow and biliary pharmacokinetics of antibiotics.

Antibiotic activity was determined by the agar plate diffusion method with medium no. 1 (BBL Microbiology Systems, Cockeysville, Md.) adjusted to pH 7.0, with Bacillus subtilis (strain 9341) as the test organism. After collection, samples were immediately refrigerated and stored at −70°C until assay. Standard curves were established with rabbit or human pooled serum and rabbit or human pooled bile, respectively.

Pharmacokinetics were calculated with reference to a one-compartment open model. The values given in the results were averaged ± standard error of the mean.

Intraoperative antibiotic levels in serum, the common bile duct, and gallbladder bile, measured 1 h after intravenous administration of the antibiotic, averaged 65.5 ± 5.0, 3,860 ± 551, and 2,552 ± 627 μg/ml, respectively. Thus, the concentration in the gallbladder bile amounted to two-thirds of that found in the common bile duct.

In the cholecystectomized patients with T-tube drainage (Table 1), the mean antibiotic serum levels decreased from 82.5 ± 10.4 μg/ml at 1 h after dosage to 2.6 ± 0.7 μg/ml at 12 h. Biological half-life was 1.23 h, with an apparent volume of distribution of 6.4 liters. A peak concentration of 2,893 ± 859 μg/ml of bile was reached during the third hour; at 12 h, the level was still 90.0 ± 25.0 μg/ml. The concentrations in bile and serum were high (30 to 50) throughout the investigation. The total recovery of apalcillin in the 12-h period was 122.5 ± 36.7 mg; i.e., 12.2% of the dose given.

Few data on the biliary elimination of apalcillin are available. A biliary recovery of 0.6 to 9.4% of the dose given has been reported in three patients (4). Our findings indicate that the apalcillin levels in T-drain bile and in intraoperatively collected bile highly exceeded the simultaneously measured serum levels.

Bile flow in patients with external biliary drainage amounted to 218 ± 29 ml in the 12-h period. Taking into account the estimated bile flow of 500 to 600 ml per day on day 8 post-cholecystectomy (6), it can be assumed that only two-thirds of hepatic bile production has been recovered by drainage. The biliary elimination of apalcillin determined by this method may therefore be underestimated.

Apalcillin levels found intraoperatively in the common bile duct were markedly higher than those in the T-drain bile. This may be due to dilution by the “dead” space of the drain lumen, but the persistence of postoperative impairment of the hepatic excretory function cannot be excluded.

The intraoperative concentrations of apalcillin in bile were higher in common duct bile than in gallbladder bile. This difference can be attributed to gallbladder disease (lithiasis, inflammation) and cystic duct obstruction, which may modify the flow of apalcillin into or across the gallbladder.

In keeping with other groups, we observed marked interindividual variation in the elimination of antibiotic in bile. Variation in bile flow, liver excretory function, and binding of the antibiotic at sites other than the liver may be considered as main factors accounting for this phenomenon.

We previously performed works on human biliary elimination of 14 other beta-lactams by the same procedure as in the present study (2, 3). An elimination of 0.02 to 0.10% of the dose given was noted for cephalotin, cephalothin, cefaclor, cefamandole, and ampicillin; from 0.10 to 0.30% elimination was noted for penicillin G, cephaloridine, cefazolin, cefuroxime, carbenicillin, and cephalaxin; the highest eliminations concerned cefotiam (1.8%), mezlocillin (2.6%), and metampicillin (8.2%). Thus, the passage of apalcillin into T-drain bile appears clearly superior to that of the other studied antibiotics. From data published previously (1, 5), a 50-μg/ml level of apalcillin appears to be sufficient for inhibition of most microorganisms responsible for biliary infections. As shown by the present study, such a concentration was widely exceeded in bile during the 12-h period after intravenous administration of 1 g of apalcillin.

The spectrum of antibacterial activity of apalcillin and its

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**Table 1.** Serum and tissue levels and bilirubin recoveries of whole animal after intravenous single injection of I g of the antibiotic to susceptible and resistant strains.
hepatotropism suggests that administration of this antibiotic may be particularly suitable for treatment of biliary tract infections, provided that there is adequate hepato-excretory function and an absence of biliary obstruction.

LITERATURE CITED