Concentrations of Kanamycin and Amikacin in Human Gallbladder Bile and Wall

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The concentrations of amikacin and kanamycin were determined in the serum, gallbladder bile, and gallbladder wall of 20 patients undergoing elective cholecystectomy. Of 20 patients, 14 received 500 mg of amikacin intramuscularly and 6 received 500 mg of kanamycin intramuscularly at various times before surgery. In patients receiving kanamycin, detectable levels appeared in bile within 90 min after drug administration, and in five of six patients concentrations ranged from 1.9 to 23 µg/ml. Levels of kanamycin in gallbladder wall ranged from 8.0 to 14 µg/g. In patients receiving amikacin, detectable levels appeared in bile within 48 min after drug administration and ranged from 1.3 to 7.5 µg/ml in 12 of 14 patients. Levels of amikacin in gallbladder wall ranged from 4.7 to 34 µg/g. The presence of an obstructed cystic duct did not preclude the entry of either antibiotic into gallbladder bile, and this may reflect passage of antibiotic through the gallbladder wall rather than accumulation via bile secretion.

This report relates the results of a study of the concentration of amikacin and kanamycin in serum, gallbladder bile, and gallbladder wall in a group of 20 patients undergoing cholecystectomy who had received one or the other of these aminoglycosides at various times before surgery.

MATERIALS AND METHODS

Patients and tissue collection. We studied 20 patients who were undergoing cholecystectomy and who had documented cholelithiasis and chronic cholecystitis. These patients ranged from 17 to 65 years of age and from 50 to 77 kg in weight; 16 were female. Preoperative determinations of total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and serum creatinine were carried out in all patients. Except as indicated below, the concentrations of creatinine, blood urea nitrogen, and liver enzymes were normal. One patient in the kanamycin group with alcoholic cirrhosis had a serum bilirubin of 2.4 mg/100 ml. One patient in the amikacin group had a serum bilirubin of 3.0 mg/100 ml secondary to cholelithiasis; four patients in this group had elevated liver enzymes (aspartate, aminotransferase, alanine aminotransferase, and alkaline phosphatase). One patient in the kanamycin group and three patients in the amikacin group had an obstructed cystic duct at surgery.

Preoperatively, 14 patients received 500 mg of amikacin intramuscularly and 6 patients received 500 mg of kanamycin intramuscularly. The exact time of drug administration was noted. One patient in the kanamycin group received two doses of kanamycin, 500 mg each, 10 h and 3 h before surgery. All other patients received one dose of preoperative antibiotic, and no patient received any other antimicrobial agent before surgery. At laparotomy, before manipulation of the gallbladder, 5 ml of bile was withdrawn by puncture of the gallbladder with needle and syringe. Simultaneously, 10 ml of venous blood was drawn from a peripheral vein. In eight patients, specimens of gallbladder wall were taken after removal of the gallbladder. The tissue was immediately rinsed in saline to remove residual bile and blood. Bile, serum, and tissue were stored at −70°C immediately after the operative procedure. For analysis of gallbladder wall tissue, the tissue was weighed and then homogenized in 0.1 M potassium phosphate, pH 8.0. Tests showed that over 90% of both amikacin and kanamycin were extracted by this technique. The results for gallbladder wall concentrations are expressed as micrograms of antibiotic per gram of wall tissue, assuming complete extraction of antibiotic into the buffer solution.

Analysis of antibiotic concentrations. Antibiotic levels were determined by Bristol Laboratories, Inc., Syracuse, N.Y., using a standard agar-plate bioassay method (4). Petri dishes were prepared with 10 ml of agar base overlaid with 4 ml of seed agar, both using media no. 5 (BBL Microbiology Systems, Cockeysville, Md.). The seed agar contained 1.5 × 10^8 spores per liter of agar of Bacillus subtilis, strain ATCC 6633 (American Type Culture Collection, Rockville, Md.). Paper disks were impregnated with 20 µl of five standard concentrations of antibiotic prepared in sterile human bile and the test solutions. Values were determined in triplicate on each of two agar plates. Plates were incubated at 35°C for 16 to 18 h. Zone diameters were then measured to the nearest 0.2 mm, using a millimeter scale. A standard curve was prepared on semilog paper, with the standard curve drawn as the straight line best fitting these points. Tests run using bile alone showed that the B. subtilis test strain was not inhibited by bile.
RESULTS

Results from the amikacin group are shown in Table 1. Specimens were taken from 48 to 420 min after antibiotic administration. Concentrations of amikacin in gallbladder bile ranged from 1.3 to 7.5 μg/ml in 12 cases and were less than 1.0 μg/ml in the remaining 2 cases. Of four patients in whom gallbladder wall levels were measured, values ranged from 4.7 to 110 μg/g. In three patients who had an obstructed cystic duct found at surgery, amikacin concentrations in gallbladder bile ranged from 1.7 to 3.4 μg/ml.

The results from the kanamycin group are shown in Table 2. Specimens were taken from 90 to 180 min after antibiotic administration. Concentrations of kanamycin in gallbladder bile ranged from <1.0 μg in one patient to 1.9 to 23 μg/ml in five other patients; the patient with the highest level had received two preoperative doses of kanamycin. The one patient with a kanamycin bile level of less than 1.0 μg/ml had alcoholic cirrhosis and a serum bilirubin of 2.4 mg/ml. Of the four patients in whom gallbladder wall levels were measured, levels ranged from 8.0 to 16.0 μg/g. One patient in this group had an obstructed cystic duct at surgery; this patient’s bile and gallbladder wall contained high levels of kanamycin.

DISCUSSION

Few studies are available documenting the penetration of aminoglycosides into gallbladder tissue or gallbladder or common duct bile. Preston et al. (2) studied kanamycin levels in T-tube bile from four human subjects and found that less than 1% of 1-g intramuscular dose was eliminated in hepatic bile; maximum bile concentrations of kanamycin ranged from 12.5 to 41.0 μg/ml. Keighly et al. (1) studied levels of gentamicin in human gallbladder bile. They found that only 2 of 40 patients had bile levels greater than 4 μg/ml, and in 28 patients gentamicin levels were <2 μg/ml. We have found no studies on gallbladder bile levels of amikacin in human subjects.

We studied 20 patients undergoing cholecystectomy for chronic and subacute cholecystitis and who received preoperative kanamycin or amikacin. Gallbladder bile levels were >1.0 μg/ml in five of six patients receiving kanamycin and in 12 of 14 patients receiving amikacin. In addition, we found high levels of the aminoglycosides in the gallbladder wall in seven of eight patients in whom wall levels were assayed. In three of four patients receiving amikacin and in two of four patients receiving kanamycin, drug levels in gallbladder wall were at least four times greater than the level found in bile. We found high levels of both aminoglycosides in bile at the earliest times of sampling after antibiotic administration (90 min for kanamycin and 48 min for amikacin). However, because there was only one sampling point for each patient, we have not attempted to draw conclusions about the distribution and biliary kinetics of the drugs in these patients.

The levels of kanamycin and amikacin that we found in bile and gallbladder wall are therapeutically significant. For kanamycin, Yu and Washington (5) found that 50% of strains of Escherichia coli, Klebsiella, and Enterobacter are inhibited at 5, 2.5, and 5 μg/ml (50% minimal inhibitory concentration). Against the same three bacteria, Reimer et al. (3) found geometric
mean minimal inhibitory concentrations of 1.5, 0.8, and 1.1 μg/ml, respectively, for amikacin. Even though these values are not strictly comparable, we think that they indicate that amikacin should be more effective than kanamycin against these gram-negative bacteria commonly found in the biliary tract.

Bile levels of both antibiotics are of particular note in patients with an obstructed cystic duct found at surgery. In the three such patients in the amikacin group, bile levels ranged from 1.7 to 3.4 μg/ml. In the kanamycin group, in the single such patient studied, the bile level was 23 μg/ml, and the wall level was 14 μg/g (this patient had received two preoperative doses of kanamycin). These data show that the presence of an obstructed cystic duct does not preclude entry of either antibiotic into gallbladder bile and suggest that the antibiotic may pass through the gallbladder wall to enter the bile as well as accumulate via bile secretions.

Even with sophisticated contemporary diagnostic and surgical techniques, sepsis frequently complicates the management of patients with biliary disease. We suggest that further studies of aminoglycoside penetration into gallbladder wall and bile are warranted, with emphasis on patients with an obstructed biliary tract.

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LITERATURE CITED