Excretion of Cefamandole, Cefazolin, and Cephalothin into T-Tube Bile

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Received for publication 9 January 1978

The biliary tract excretion of cefamandole, cefazolin, and cephalothin was measured in eight patients with T-tubes inserted into their common ducts after ductal exploration for biliary tract stones. Each patient received 1.0 g intravenously of each cephalosporin on 3 separate days; T-tube bile and serum were collected at selected time intervals thereafter. In seven patients, bile and urine were collected for 6 h after the administration of each drug. Mean peak levels of cefamandole, cefazolin, and cephalothin in bile were 352, 46, and 12 μg/ml, respectively. The respective mean peak serum levels were 55.0, 92.8, and 32.4 μg/ml. Despite the fact that peak serum levels of cefazolin were 1.5 times those of cefamandole, levels in bile of cefamandole were about 8 times those of cephalothin. Over a 6-h period, almost three times as much cefamandole was excreted into bile as was cefazolin. Therefore, in those patients with biliary tract sepsis, in whom a cephalosporin is indicated for therapy, cefamandole appears to be the drug of choice.

Enteric bacteria, especially the Enterobacteriaceae and streptococci, are the most frequent causes of suppurative biliary tract disease (1). Thus, antimicrobial therapy of acute cholecystitis and acute cholangitis could logically include agents such as ampicillin, cephalosporins, and aminoglycosides. Indeed, several investigators have demonstrated that in the absence of obstruction, ampicillin (2), cephaloridine, cefazolin (4), and cephalaxin (5) are excreted into bile in concentrations above those necessary to inhibit most susceptible bacterial pathogens causing biliary tract infections.

Cefamandole is a new semisynthetic cephalosporin derivative with a broad spectrum of antibacterial activity against a wide variety of gram-positive and gram-negative bacteria (3). In fact, on a weight basis, cefamandole appears to be more active then cephalothin, cephaloridine, cefazolin, and cephalaxin against gram-negative bacteria (3). Therefore, cefamandole would be a logical choice for the antimicrobial therapy of suppurative biliary tract disease if it were excreted in adequate concentrations into human bile. The purpose of the present investigation was to study the biliary tract excretion of cefamandole and to compare it to that of cephalothin and cefazolin.

MATERIALS AND METHODS

Eight patients, 31 to 89 years of age, requiring T-tube drainage of their common duct, were studied. Starting 1 week after surgery, each patient received 1.0 g of cephalosporin derivative. On separate days, at least 48 h apart, cefamandole nafate, cephalothin, and cefazolin were given intravenously (i.v.). Serum and bile were obtained before and at 30, 60, and 120 min after administration of drug. In seven patients, bile was collected for the 6-h period after administration of each drug.

All patients had adequate renal function (creatinine, ≤ 1.6 mg/100 ml), no history of allergy to cephalosporins, and no evidence of jaundice at the time of the study.

All specimens of serum and bile were frozen at −70°C immediately and assayed within 48 h of collection. The antibiotics were assayed microbiologically by an agar well diffusion method with the use of spores of Bacillus subtilis ATCC 6633 as the indicator organism. The spores were collected from agar inoculated with vegetative forms and incubated at 37°C for 7 days. By means of a previously described technique (4), the spores were added to molten heart infusion agar (Difco) to make agar plates impregnated with the indicator organism.

Stock solutions of antibiotic were freshly prepared. Standard solutions of cephalosporins, as well as serum specimens, were diluted in human serum for the assays of these drugs in serum. Phosphate buffer (pH 6.0) was used to dilute the antibiotic standards and bile specimens for the assays of drug in T-tube bile. (Cephalosporins diluted in normal bile or phosphate buffer give identical zone sizes [4].)

Into 6-mm-diameter agar wells, 20 μl of the appropriate dilution of test material was added with an Oxford microliter pipette. The plates were incubated at room temperature for 6 h and overnight at 37°C.
Zones of inhibition were read after 24 h, and antibiotic levels were calculated from simultaneously prepared standard curves. Results are expressed as means plus and minus their standard errors.

RESULTS

The mean concentrations of cefamandole, cefazolin, and cephalothin in bile and serum after a single 1.0-g dose given i.v. are shown in Fig. 1 and 2, respectively. Peak biliary tract concentrations for each of the cephalosporins appeared 30 min after i.v. administration. At all time intervals cefamandole reached higher levels than did either of the other two cephalosporins, with mean peak biliary levels of cefamandole of 352 ± 64 and 193.4 ± 47 μg/ml at 30 and 60 min, respectively. Whereas biliary levels of cefazolin were significantly greater than those of cephalothin at all time intervals, they were well below those of cefamandole. Cefamandole was concentrated in bile; at each time interval significantly more drug was present in bile than in serum. Indeed, at 30 and 60 min, cefamandole concentrations in bile were six to seven times greater than those in serum.

Serum concentrations of the cephalosporins did not seem to be the determining factor for the amount of drug excreted into bile. Whereas the differences in cefazolin and cephalothin levels in bile were almost directly related to their differences in serum concentrations, for cefamandole this was not the case since at each time interval the biliary levels of this drug far exceeded the serum levels.

For 6 h after administration of each drug, the total T-tube bile was collected from seven patients to determine the cumulative amount of antibiotic excreted into the biliary tract during this time period. Table 1 shows that more cefamandole than either cefazolin or cephalothin appeared in T-tube bile during this time interval. In fact, the ratio of cefamandole to cefazolin and

![Graph](http://aac.asm.org/page/169534254684/169534254684.png)

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**Fig. 1.** Mean levels of cephalosporins and their standard errors in T-tube bile after a single 1.0-g dose given i.v.

**Fig. 2.** Mean levels of cephalosporins and their standard errors in serum after a single 1.0-g dose given i.v.

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Total drug excreted (mg)</th>
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<tbody>
<tr>
<td>Cefamandole</td>
<td>4.12 ± 0.9a</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1.2 ± 0.21</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>0.25 ± 0.05</td>
</tr>
</tbody>
</table>

*a* Standard error of mean.
cephalothin excreted was 2.9 and 18 to 1, respectively.

DISCUSSION

Cephalosporins have three potential roles for use in biliary tract disease: (i) chemoprophylaxis for wound infections after cholecystectomy (6), (ii) initial therapy for suppurative biliary tract disease in patients allergic to ampicillin, and (iii) primary therapy for suppurative biliary tract disease due to organisms resistant to ampicillin.

Stone et al. have shown (6) that short-term prophylaxis with a cephalosporin significantly reduced the incidence of postoperative wound infections after elective cholecystectomy. Although most studies have clearly shown that an obstructed biliary tract precludes the excretion of any antibiotic into bile (2, 4), a patent biliary tree is likely to contain high concentrations of cefamandole even after a single dose. Thus, if a high concentration of antibiotic at the site of tissue trauma is useful in preventing postoperative wound infection, cefamandole would have distinct advantages over cephalothin and even over cefazolin.

Cefamandole has a broader spectrum of antibacterial activity than does either cephalothin or cefazolin in that it is more active against most members of the Enterobacteriaceae. Moreover, cefamandole has activity against a number of species that are resistant to cephalothin and cefazolin, such as certain strains of Escherichia coli, indole-positive Proteus, Serratia, and Enterobacter aerogenes. Most of the Enterobacteriaceae and streptococci susceptible to presently available cephalosporins are usually inhibited or killed by concentrations equal to or below 25 μg/ml. However, at the concentrations of cefamandole reached in the biliary tree, its spectrum might be extended to include some strains of Providencia and Herellea not likely to be inhibited by the lower concentrations of cephalosporins (3). For these reasons, when a cephalosporin is chosen either to prevent or treat infections of the biliary tree, cefamandole would seem to be the drug of choice.

ACKNOWLEDGMENT

This work was supported by a grant from Eli Lilly & Co., Indianapolis, Ind.

LITERATURE CITED