Biliary Tract Excretion of Cefazolin, Cephalothin, and Cephaloridine in the Presence of Biliary Tract Disease

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The biliary tract excretion of three cephalosporins, cefazolin, cephaloridine, and cephalothin, was compared in patients with biliary tract disease. In the absence of obstruction, mean antibiotic levels in bile from gall bladder and common duct in patients undergoing cholecystectomy were highest for cephalothin (17 and 31 μg/ml, respectively) than either cephaloridine (7 and 9 μg/ml) or cefazolin (1 and 4 μg/ml). Biliary tract levels generally paralleled serum levels. In no patient with cystic duct obstruction were any of the cephalosporins detectable in appreciable amounts in gall bladder bile. In patients with T-tube drainage given each of the three different cephalosporins on separate days, concentrations of cefazolin in bile were many-fold higher than either cephaloridine or cephalothin. Peak levels of cefazolin in T-tube bile averaged 51 μg/ml after intravenous and 26 μg/ml after intramuscular administration, whereas mean peak levels of cephalothin and cephaloridine were only 6 and 16 μg/ml, respectively. Here, too, T-tube levels reflected serum concentrations and obstruction to biliary flow impaired excretion of each of the drugs.

The correct choice of an antimicrobial drug for the therapy of suppurrative biliary tract disease depends in a general sense upon two factors: the antimicrobial susceptibility pattern of the etiological agent, and the likelihood that the chosen antimicrobial will reach the site of the infection.

Studies of the bacteriology of biliary tract infections have repeatedly demonstrated Enterobacteriaceae to be the most frequent etiologic agents, with Escherichia coli accounting for the great majority (5). Thus, antimicrobial agents such as ampicillin or the cephalosporins would be logical choices for therapy of biliary tract infections depending upon their delivery in adequate concentrations into human bile. Several investigators have demonstrated that in the absence of obstruction, ampicillin is readily excreted into human bile in concentrations well above those necessary to inhibit susceptible coliform bacteria (2, 7). In separate studies, cefazolin (9), cephalaxin (11), cepheactite (3), and cephalothin (10) have been measured either in gall bladder or common duct bile of patients undergoing biliary tract surgery. In the absence of obstruction, each of these drugs, except cepheactite, was shown to reach concentrations adequate to inhibit most organisms causing biliary tract infections. The purpose of the present investigation was to compare the biliary tract excretion of three parenterally administered cephalosporin derivatives, cephalothin, cephaloridine, and cefazolin. The study was designed not only to study the excretion of these antibiotics among different patients but also to compare the biliary tract levels of each of these drugs in the same patient.

MATERIALS AND METHODS

Patients. Group 1. Fifteen patients undergoing cholecystectomy for cholelithiasis or a nonfunctioning gall bladder after a standard double-dose, oral cholecystogram received 1 g of cephalothin, cefazolin, or cephaloridine at the time of induction of anesthesia. Serum samples for antibiotic determination were taken just before, and 15, 30, and 60 min after administration of the drug. Gall bladder bile was aspirated directly from the gall bladder at the time of its removal, and common duct bile was sampled when the surgeon performed the intraoperative cholangiogram. An additional serum specimen was obtained at the time of common duct aspiration.

Group 2. Eight patients (A through H) requiring T-tube drainage of their common duct were studied. Seven subjects (A through G) completed the study. Starting on postoperative day 4, each patient received 1 g of cephalosporin derivative. On separate days, 48 h apart, cephaloridine was given intramuscularly, cephalothin intravenously, and cefazolin both intravenously and intramuscularly. Serum and bile were obtained before and 30, 60, and 120 min after administration of the drug. Liver function tests (alkaline
phosphatase, serum bilirubin, and serum glutamic oxaloacetic transaminase) were entirely normal both before and during the study in patients B, C, F, and G. All liver function tests were performed by a Technicon SMA 12/60. Upper limits of normal were: alkaline phosphatase, 85 IU; serum bilirubin, 1.0 mg per 100 ml; serum glutamic oxaloacetic transaminase, 40 Karmen Units. Patients A, D, and E had persistently elevated alkaline phosphatases (150 to 200) during the course of the study. In addition, patient A had a bilirubin of 3.4 mg per 100 ml during the days he received cefazolin, and 1.9 and 1.2 mg per 100 ml on the days he received cephalothin and cephaloridine, respectively. Patient D had a bilirubin between 1.8 and 2.5 during the 4 study days, and patient E was jaundiced with a bilirubin of 4.0 to 4.5, during the entire study period.

Only patients with normal renal function (creatinine <1.1 mg per 100 ml) and no history of allergy to penicillin or the cephalosporins were included in the study.

Samples. All specimens of serum and bile were frozen immediately after collection and stored at -20 C until assayed.

Microbiological assay. The antibiotics were assayed microbiologically by a paper-disk agar diffusion method with the use of Bacillus subtilis ATCC 6633 as the indicator organism. The organism was grown on agar at 37 C for 7 days; the visible growth consisting largely of spores was harvested with sterile distilled water, heated to 65 C for 30 min to kill vegetative cells, and stored at 4 C. Assay plates were prepared by the addition of 0.1 ml of the spore suspension containing 10⁸ colony-forming units per ml to each 100 ml of molten antibiotic medium no. 2 (Difco) and cooled to 55 C, followed by the distribution of 10 ml of this seeded agar to each petri dish. Plates were stored at 5 C and used within 2 weeks of preparation.

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. After several experiments clearly demonstrated that each of the cephalosporins, diluted either in human bile or phosphate buffer (pH 6.0), gave identical zone sizes, the phosphate buffer was used to dilute both the antibiotic standards and the bile for all assays of biliary tract specimens.

Onto 6-mm diameter filter paper disks (Schleicher and Schuell) 20 μl of the appropriate dilution of the test material was added with an Oxford microliter pipette. Four disks were added to each plate; the plates were inverted and incubated at 37 C. Zones of inhibition were read after 24 h, and antibiotic levels were calculated from simultaneously prepared standard curves.

RESULTS

Group 1 patients. The concentrations of each of the cephalosporins in bile from the gall bladder and common duct plus serum, collected simultaneously with aspiration of the common duct, are presented in Fig. 1. Serum levels of cefazolin, after either intramuscular or intravenous administration, were generally higher than those of cephaloridine or cephalothin. For the most part, common duct levels of the cephalosporins paralleled those levels attained in the serum. Thus, both the highest serum and com-
mon duct levels were achieved after administration of cefazolin. However, in one patient, M.S., who excreted only 6 μg of cefazolin per ml into his common duct at 30 min despite a simultaneous serum level of 70 μg/ml, there was marked narrowing of the distal end of his common duct due to a stricture. It is likely that the obstruction due to this stricture accounted for the relatively low levels of cefazolin excreted into his common duct, since M.S. was studied postoperatively after common duct exploration and T-tube drainage relieved his obstruction. This time his T-tube bile at 30 min reached a level of 18 μg of cefazolin per ml after an identical 1-gram intravenous dose (patient D, Fig. 2).

The cephalosporin concentrations measurable in gall bladder bile mostly paralleled those levels attained in common duct bile except where severe cholelithiasis and/or obstruction of the cystic duct were present. This was true of patients M. H. and S. K. in the cefazolin intramuscular group and Y. B. in the cephalothin intravenous group. Each of these patients contained less than 1 μg of the cephalosporin derivative per ml in gall bladder bile despite common duct levels well above that amount.

**Group II patients.** The design of this part of the study was to give each patient 1 g of each cephalosporin and compare the biliary tract excretion of the three drugs in each individual. In this way every patient served as his own control. Figures 2 and 3 present the biliary tract and serum concentrations of the drugs in each person with respect to time. The highest serum and biliary tract levels were achieved with cefazolin given either intravenously or intramuscularly. Of the seven patients who completed this study, six excreted cefazolin in

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**Fig. 2.** Common duct (T tube) levels of cephalosporins after a 1.0-g dose, group 2 patients.
concentrations equal to or many-fold greater than either cephaloridine or cephalothin (Fig. 2). In fact, except for patients A and E, peak cefazolin concentration in T-tube bile were at least double those of either of the other cephalosporins; cephaloridine achieved higher levels in bile than did cephalothin in all but patient D (Table 1). Peak serum levels of cefazolin were consistently the highest in all patients but patient A, whose serum levels of cephaloridine and cefazolin were equal. In addition, it should be noted the patient B, after intravenous cefazolin, achieved a peak level of 85 μg/ml in his T-tube drainage, whereas his peak serum concentration was only 70 μg/ml. Moreover, patient G also seemed to concentrate cefazolin in his bile. After intravenous and intramuscular doses of cefazolin, patient G excreted peak concentrations of 168 and 80 μg/ml, respectively, into his bile, whereas peak serum concentrations of cefazolin were 56 and 52 μg/ml, respectively. Only one patient, C, excreted a higher concentration of cephaloridine into his T tube then he achieved in his serum.

Two patients, A and E, consistently failed to excrete high levels of cefazolin into the common duct despite high serum levels. Patient E continued to have biliary obstruction throughout the study period; his T tube drained poorly and his bilirubin and alkaline phosphatase remained elevated. Patient A was obstructed intermittently during the study; on the days he received cefazolin his bilirubin was above 3.0 mg per 100 ml and his T tube drained poorly. In addition, patient F failed to attain high biliary-tract levels of cefazolin after an intravenous dose. This was unexplained since his serum

**TABLE 1.** Peak serum and T-tube bile concentrations of cephalosporins in group 2 patients after a 1.0-g dose

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drug and route of administration*</th>
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<tbody>
<tr>
<td></td>
<td>Cefazolin i.v.</td>
</tr>
<tr>
<td>A</td>
<td>49/5*</td>
</tr>
<tr>
<td>B</td>
<td>70/85</td>
</tr>
<tr>
<td>C</td>
<td>88/80</td>
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<tr>
<td>D</td>
<td>80/25</td>
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<tr>
<td>E</td>
<td>65/5</td>
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<td>F</td>
<td>40/10</td>
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<tr>
<td>G</td>
<td>56/168</td>
</tr>
<tr>
<td>H</td>
<td>69/27</td>
</tr>
</tbody>
</table>

* i.v., Intravenous; i.m., intramuscular.

* Serum level/T-tube level (in micrograms per milliliter).
levels were quite high and his liver function was within normal limits throughout the study period. Most of the other patients who received cefazolin, either intramuscularly or intravenously, or cephaloridine achieved levels in the bile more than adequate to eliminate susceptible Enterobacteriaceae responsible for biliary tract sepsis and maintained these levels over some time. On the other hand, only one patient achieved concentrations of cephalothin adequate to treat these infections. Cephalothin is so rapidly cleared from serum by the kidney that it is not surprising that in the presence of normal renal function little appears in the bile.

**DISCUSSION**

Since the demonstration first that tetracycline (1) and then ampicillin (2, 7) were readily excreted into the biliary tract in the absence of common duct obstruction, these agents have been the drugs of choice for therapy of biliary tract infections. The emergence of enteric bacteria which carry factors conferring resistance to many antibiotics, including tetracycline and ampicillin, and the occasional patient allergic to the penicillins have led to a search for other antibiotics which are readily excreted into the biliary tree and are likely to have antibacterial activity against most of the bacteria responsible for supplicative biliary tract disease. Sales et al. (11) gave cephalaxin, an orally administered cephalosporin, to 24 patients before and after gall bladder and/or common duct surgery and demonstrated that the drug reached peak levels in common duct bile at 3.5 h after administration, with a mean of 3.0 μg/ml. Some patients achieved levels as high as 12 μg/ml. Probenecid, given to block renal excretion of cephalaxin in five patients, significantly raised cephalaxin levels in the bile. In addition, patients with functioning gall bladders developed high levels (14 to 92 μg/ml) of cephalaxin in gall bladder bile after multiple doses of the drug before surgery. Brogard et al. (3) investigated the biliary tract excretion of cepheactril, an investigational cephalosporin, and demonstrated disappointingly low levels of antibiotic in human common duct bile after a 1.0-g dose. It was not recommended for use in biliary tract infections. More recently, Ram and Watanatittan (9) measured cefazolin in gall bladder and common duct bile after various dosage schedules of the drug and demonstrated, as we have, that cefazolin is readily excreted in its active form by the liver. In addition, Ram and Watanatittan (10) studied the biliary tract excretion of cephalothin in several settings and found that after a total dose of 8 g of the drug, normal subjects as well as those with chronic cholelithiasis and/or gall bladder biliary tract disease received cefazolin both in common duct and gall bladder bile. In fact, eight of ten patients with chronic biliary tract disease developed levels of cephalothin above 100 μg/ml in gall bladder bile, whereas serum levels ranged between 0.81 and 22.9 μg/ml. In addition, common duct bile contained concentrations between 5.8 and 192 μg/ml, with a mean of 47.7 μg/ml. Although the serum levels of cephalothin in our patients were comparable to those in Ram and Watanatittan’s patients, gall bladder and common duct bile levels were only 1 ± 0.7 and 4.0 ± 5 μg/ml, respectively. One reason for the disparity between these results is that we collected bile after a single 1.0-g dose, whereas Ram and Watanatittan measured biliary tract levels after a total dose of 8 g. Although it is conceivable that after multiple doses the drug is stored in the liver and excreted quite slowly, it is unlikely, since we demonstrated that the drug appeared in common duct bile promptly after intravenous administration, peaked within 30 min, and was almost undetectable at 2 h.

Ram and Watanatittan (10) also measured T-tube levels at 2-h intervals after a single 2.0-g intravenous dose of cephalothin. Their peak at 2 h was almost 7 μg/ml, whereas T-tube bile levels in our patients after a 1.0-g dose was only 1.0 ± 0.2 μg/ml at 2 h. On the other hand, we demonstrated a rapid excretion of cephalothin into bile with peak at 6 ± 5 μg/ml reached 30 min after the intravenous dose. It is conceivable that Ram and Watanatittan would have measured even higher concentrations of cephalothin at 30 to 60 min after their 2.0-g dose had bile been sampled at that time.

An additional study of the biliary excretion of cephalothin was reported by Brogard et al. (4). These authors demonstrated mean peak T-tube levels of 15.5 μg/ml (with a range of 0.4 to 42 μg/ml) between 1 and 3 h after a 1.0-g dose intravenously. However, of the 10 patients studied, four failed to excrete a concentration above 3.5 μg/ml at any time during the study, and three others had peak levels of 15, 18, and 21 μg/ml. Except for four patients who excreted cephalothin in high concentrations (24 to 42 μg/ml), their results were comparable to ours.

It should not be surprising that in the search for an effective drug for supplicative biliary tract disease, gentamicin has received some attention (6, 8, 12). Although the majority of organisms associated with biliary tract infection are inhibited by levels of gentamicin attainable in serum without ototoxicity. very
few are inhibited by the uniformly low levels measured in the gall bladder (8). For this reason, gentamicin does not seem to be a logical drug to use for biliary tract infections despite the uniform susceptibility of the etiological agents.

The present study was an attempt to evaluate the excretion into bile of three presently available parenteral cephalosporins. By using each patient as his own control, we were able to compare the three drugs with a minimum of variables. In our hands, cefazolin, after either intravenous or intramuscular administration, was superior to either cephaloridine or cephalothin in achieving higher and more sustained levels in common duct bile. The explanation for this seemed to be directly related to the higher and more sustained levels of cefazolin achieved in serum. It would seem, then, that if the decision is made to choose a cephalosporin for the therapy of a biliary tract infection, cefazolin would be a logical first choice. Nonetheless, it should be pointed out that despite the seemingly rapid and prolonged excretion of cefazolin into human bile, the presence of obstruction to bile flow, either into the gall bladder or common duct, markedly reduces the appearance of any antibiotic, as demonstrated by this and several other studies (1, 7, 11).

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LITERATURE CITED