Biliary Levels of Ceforanide

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Ceforanide levels in plasma, gallbladder bile, gallbladder tissue, and common bile duct were studied in 10 patients with normal biliary tracts and in 35 patients with biliary disease at various intervals after intravenous injection of 1 g of the drug. Peak blood levels were obtained within 1 h of administration (mean, 67 ± 15 μg/ml). Patients with a normal biliary tract, as well as patients with chronic cholecystitis and a patent cystic duct, achieved high gallbladder bile levels of ceforanide within 2 h (mean, 76 ± 25 μg/ml) and attained even higher levels by 4 h (mean, 182 ± 51 μg/ml). However, all patients with chronic cholecystitis and an occluded cystic duct had very low drug concentrations in the gallbladder bile (14 ± 7 μg/ml at 2 h). Despite this difference in gallbladder bile levels, ceforanide levels of 21 ± 3 μg/g were achieved at 1 to 3 h in gallbladder tissue in both groups with chronic cholecystitis. The concentration of ceforanide in common bile duct was 149 ± 59 μg/ml at 2 h after administration, with levels over 60 μg/ml present from 1 to 4 h after administration. These results indicate that ceforanide reaches high levels in the biliary tract. Its potential value in the prevention and treatment of biliary infections should be assessed.

Infections of the biliary tract are usually caused by Enterobacteriaceae and streptococci (2). Accordingly, antimicrobial therapy for the treatment of acute cholecystitis and cholangitis could include a cephalosporin. Ceforanide is a recently discovered semisynthetic cephalosporin with activity against gram-positive cocci and common gram-negative bacilli equal to or greater than those of the older cephalosporins and a somewhat longer half-life in plasma. If ceforanide reaches the bile and the tissues of the biliary tract in effective concentrations, this antibiotic could be useful in the treatment of biliary tract infections and in the prevention of such infections in patients undergoing surgical procedures. This study was undertaken to assess the levels of ceforanide in plasma, bile, and gallbladder tissue in human subjects undergoing operative procedures.

MATERIALS AND METHODS

Ceforanide (BL-786R) was provided as a sterile sodium-free mixture of this cephalosporin and lysine (Bristol Laboratories, Syracuse, N.Y.).

The study group included patients admitted to the Surgical Services of the Veterans Administration Medical Center and the University of Kentucky Medical Center, Lexington. Informed consent was obtained from all participants. Patients were divided into three groups: (i) those with known biliary disease (n = 10); (ii) those undergoing cholecystectomy for gallbladder disease (n = 30), further subdivided on the basis of radiological findings into those with a nonobstructed cystic duct (n = 20) and those with an obstructed cystic duct (n = 10); and (iii) those who underwent a common bile duct (CBD) exploration for their primary disease and had a T-tube placed in the duct for drainage (n = 15).

Patient data. All patients were men. The mean years of age ± standard error of the mean in the groups were: group I, 46 ± 5; group IIa, 55 ± 3; group IIb, 60 ± 4; and group III, 66 ± 18. The mean weights (lbs.) ± standard error of the mean were: group I, 162 ± 11; group IIa, 185 ± 7; group IIb, 195 ± 10; and group III, 148 ± 10. Group I (without biliary tract disease) included eight patients with chronic duodenal ulcers who underwent vagotomy and gastric drainage, one patient with morbid obesity who underwent gastric bypass, and one patient with gastric cancer who underwent subtotal gastrectomy. None of the patients in this group had any biliary symptoms and all had normal biliary tracts at operation. All patients in group II (a and b) had symptomatic gallstones and underwent cholecystectomy. Histological examination of the gallbladder revealed chronic cholecystitis in all. Three patients in this group also had stones in the CBD at the time of operation. They underwent CBD exploration in addition to cholecystectomy, and a T-tube was left in the duct. Patients in groups I and II were studied intraoperatively. Patients in group III included two of the three patients referred to above and an additional three patients. The latter three patients had cholecystectomy performed before this hospitalization and were operated on for relief of stones in CBD on this occasion. These three also had T-tubes in their CBD. The group III patients were studied 5 to 7 days after operation when their liver functions (as determined by serum values of total bilirubin, serum glutamic oxal-
acetic transaminase, serum glutamic pyruvic transaminase, and alkaline phosphatase) were normal. The timing of this study was such that abnormalities in liver function due to the preexisting stones in the CBD, operative trauma, and anesthetic agents would not affect measurements of ceforanide levels. A T-tube cholangiogram was done routinely to make certain that there was no CBD obstruction that would affect antibiotic excretion. There was no evidence of obstruction at the time of study.

Dose, samples, and timing. All patients were studied after a single 1-g dose of ceforanide given by intravenous (i.v.) infusion over 10 min. Patients in groups I and II were started preoperatively on an i.v. drip of 5% dextrose in 0.5 N saline. The drug was then injected through the i.v. infusion. In groups I and II, the timing of the administration of ceforanide was such that it would precede the actual sampling in the operating room. In different patients, the antibiotic was thus given either 1, 2, 3, or 4 h before the expected sampling time. The operation was then started, and the samples were obtained at the desired time in each group of patients. All patients received premedication with 75 mg of meperidine, 0.3 to 0.5 mg of atropine, and 10 mg of diazepam given intramuscularly 1 h before the operation. Anesthesia was achieved in all the patients by i.v. induction with sodium thiopentone (3 mg/kg), followed by injection of 3 mg of tubocurarine chloride and 100 mg of succinyl choline. Endotracheal intubation was followed by maintenance of anesthesia with a mixture of 60% nitrous oxide and 40% oxygen and controlled ventilation. Supplemental analgesia was obtained with 1 to 1.5% enflurane in gas mixture or i.v. injection of 1 to 5 ml of fentanyl citrate (0.05 mg/ml) or 0.02 to 0.09 mg of pancuronium bromide per kg. None of the patients was operated on under halothane anesthesia. In group I, only samples of plasma and gallbladder bile were obtained. Peripheral blood was drawn, and plasma was separated by centrifugation. Gallbladder bile was obtained by inserting a 23-gauge needle into the gallbladder through a subserosal tract, and 2 to 3 ml of bile aspirated. The insertion of the needle was made through the subserosal tract to avoid biliary leakage into the subcapsular cavity. The group II patients, whose gallbladders were aspirated, did not present similar sampling opportunities. The samples of plasma, gallbladder bile, CBD bile, and gallbladder tissue were obtained. In this group, since the gallbladder was to be removed because of the disease, the needle was directly inserted into the gallbladder at the time of the sampling. CBD bile was obtained by inserting a 23-gauge needle into the duct and aspirating the bile. The gallbladder was removed at the time of the sampling and a 2 to 3-g tissue sample was obtained. Any free bile was washed out from the wall. In group III patients, simultaneous samples of plasma and CBD bile were obtained at 1, 2, 4, 6, 8, and 12 h after i.v. administration of 1 g of ceforanide as described previously.

All plasma and bile samples were chilled after collection and maintained at -16°C until assay. Not all samples could be obtained from all patients at the exact time planned, due to technical difficulties. The gallbladder tissue was frozen immediately after sampling and was maintained at -16°C until assay. The frozen sample was then rinsed in distilled water and blotted dry on filter paper. The dried specimen was then immersed in liquid nitrogen and pulverized with a stainless steel punch and die. The stainless steel punch was kept on dry ice during pulverization. A 1-g sample of pulverized tissue was then mixed with 4 ml of distilled water and thoroughly homogenized. During homogenization, the mixture was kept chilled in ice. A 0.5-ml amount of the homogenate was then added to 1 ml of acetyl nitrile and 0.1 ml of 6% trichloroacetic acid, mixed, and centrifuged. The supernatant was decanted and washed with 5 ml of methylene chloride and then used for assay of ceforanide.

The following laboratory studies on blood and urine were performed 24 h before and 24 to 48 h after administration of ceforanide to determine the effects of this agent on liver and kidney function: hemoglobin, hematocrit, total leukocytes, differential, and platelet counts; total bilirubin, transaminases, alkaline phosphatase, lactate dehydrogenase, creatinine, and blood urea nitrogen of serum; urinalysis, including tests for sugar, albumin, casts, and specific gravity.

Concentrations of ceforanide in plasma and bile were determined in four patients by the cylinder plate bioassay and in all others by high-pressure liquid chromatography. Tissue ceforanide levels were determined by the cylinder plate bioassay method. The sensitivity of the assay methods for plasma and bile were 2 μg/ml and for gallbladder tissue 1 μg/ml. The reproducibility of the assay was 3.2% for replicate samples. Recovery of the added drug was 88 ± 2% from plasma and bile and 94 ± 3% from gallbladder tissue.

RESULTS

None of the patients in this study experienced complications or died during their hospitalization. The needle aspiration of gallbladder and CBD did not result in leakage of bile. There was no evidence of change in liver or kidney function after administration of ceforanide.

The results of the ceforanide assay in plasma, gallbladder bile, CBD, and gallbladder tissue are shown in Table 1. Levels of ceforanide in plasma (67 ± 15 μg/ml) peaked at 1 h after administration with a steady decline thereafter. Ceforanide levels in the gallbladder bile of patients with patent cystic ducts (patients with normal biliary tracts and those with chronic cholecystitis whose gallbladders were visualized on cholecystography) steadily increased from a mean of 18 μg/ml at 1 h to 182 μg/ml at 4 h. At 4 h after administration of the drug, the gallbladder bile level was nearly six times the plasma level. However, in patients with chronic cholecystitis and obstructed cystic ducts the levels of ceforanide in gallbladder bile were low. Despite these differences between the two groups of patients with chronic cholecystitis (patent and obstructed cystic ducts), the levels of ceforanide in gallbladder tissue were high and similar in both groups (mean, 20 ± 3 μg/g) at 1, 2, and 3 h and (mean, 10 ± 2 μg/g) at 4 h. Levels of ceforanide in the CBD were variable; they were higher in group IIa than in group IIb.

The relationships between concentrations of
TABLE 1. Ceforanide levels

<table>
<thead>
<tr>
<th>Patient group (n)</th>
<th>Sampling time (h)</th>
<th>Concentration (µg/ml) of ceforanide in:</th>
<th>Concentration (µg/g) of ceforanide in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>Gallbladder</td>
</tr>
<tr>
<td>I (10)</td>
<td>1</td>
<td>67 (2) ± 15</td>
<td>29 (2) ± 29</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>43 (4) ± 3</td>
<td>131 (2) ± 61</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>32 (3) ± 3</td>
<td>70 (3) ± 54</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>26 (1)</td>
<td>341 (1)</td>
</tr>
<tr>
<td>IIa (20)</td>
<td>1</td>
<td>55 (6) ± 5</td>
<td>14 (6) ± 6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>45 (6) ± 4</td>
<td>49 (6) ± 16</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>30 (3) ± 2</td>
<td>101 (4) ± 33</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>30 (4) ± 3</td>
<td>142 (4) ± 41</td>
</tr>
<tr>
<td>IIb (10)</td>
<td>1</td>
<td>42 (3) ± 7</td>
<td>6 (3) ± 5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>38 (4) ± 4</td>
<td>14 (4) ± 7</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>31 (2) ± 2</td>
<td>29 (1)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>17 (1)</td>
<td>0 (1)</td>
</tr>
</tbody>
</table>

* After injection of ceforanide.

* Numbers in parentheses represent the number of patients providing data at indicated time period. Mean ± standard error of the mean.

* Patients with patent cystic ducts.

* Patients with obstructed cystic ducts.

ceforanide in plasma and bile were established in five patients who had T-tubes placed in the CBD (Fig. 1). Significant plasma levels of ceforanide were obtained even at 12 h after injection (15 ± 3 µg/ml).

DISCUSSION

These results show that ceforanide reaches high concentrations in the biliary tract in patients without biliary disease and in those with chronic cholecystitis and cholelithiasis. In patients with non-obstructed cystic ducts, levels of ceforanide in gallbladder bile 2 to 4 h after dosage were two to six times the concentrations in plasma.

The levels of ceforanide in gallbladder bile in patients with obstructed cystic ducts were low. Since bile is not reaching the gallbladder, the drug probably reaches the lumen by diffusion from the blood stream and the wall. Hence the drug concentration is much lower than in the group with a patent duct. The data also indicate that when the CBD is similarly obstructed, the level in CBD bile also will be low.

The levels in gallbladder tissue were similar whether the cystic duct was patent or not. This suggests that the level of the drug in the gallbladder tissue is probably dependent on diffusion from blood rather than absorption from the luminal contents. At no time did the gallbladder tissue level exceed serum level.

Our studies show that ceforanide levels in plasma remain high for considerable time: 10 to 15 µg/ml at 12 h after administration, confirming previous studies on the long half-life of this agent (7). These levels are much higher than the minimum inhibitory concentrations for common pathogens. Although ceforanide is predominantly excreted in the urine (7), our data show that like other cephalosporins it reaches high concentrations in bile (1, 3–6).

In clinical practice, it seems logical to use antibiotics which reach high biliary levels in the management of biliary infection. Data from animal studies, which are mostly performed on a normal hepatobiliary tree, cannot be applied to the studies of the human biliary tract. Techniques of obtaining human bile samples are also different. Duodenal aspiration is a poor technique because the bile sample is mixed with gastric and duodenal secretions, and the pH is also different. The present study used both perioperative sampling and T-tube sampling. In the former, only single samples can be obtained. By varying the time of drug administration in relation to surgery, samples at different times can be obtained as was done in this study. The T-tube studies permit evaluation of the kinetic relationship of blood levels to CBD levels. Neither method allows for correlation between drug concentration in bile and bile flow. Similarly, in the human it is not feasible to calculate total drug excretion or clearance because there is no safe way to measure total bile flow. The clearance of a drug, such as ceforanide, in bile will depend on numerous considerations such as rate and vol-
volume of distribution in intravascular and extracellular compartments, protein binding, hepatic function, urinary excretion, etc. These limitations do not detract from studies of drug concentration alone. In therapeutic situations, concentration and time of excretion, rather than total recovery, are important in determining use.

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LITERATURE CITED