Biliary and Pancreatic Excretion of Cefamandole

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After intravenous infusion of secretin and cholecystokinin in six dogs, cefamandole (50 mg/kg of body weight) was given intravenously for 10 min. Samples of serum, bile, pancreatic juice, liver, pancreas, fat, and muscle were collected over a 2-h period. Cefamandole levels were measured by a microbiological assay. The highest levels were as follows: serum, 160 μg/ml; bile, 3,071 μg/ml; pancreatic juice, 7 μg/ml; liver, 101 μg/g; pancreas, 44 μg/g; muscle, 20 μg/g; and fat, 14 μg/g. Levels in pancreatic juice were extremely low compared with levels in pancreatic tissue, suggesting the existence of a barrier to excretion at the ductal membrane.

Cefamandole is excreted in bile at high concentrations (1, 5–9, 11, 13) and may therefore be useful in the treatment and prophylaxis of biliary tract infections. In contrast, low levels of cefamandole in pancreatic juice have been reported (3, 12). It is uncertain whether this antibiotic achieves therapeutic levels in pancreatic tissue. In the present study, we measured cefamandole levels in the livers and pancreases of anesthetized dogs and compared these with levels in serum, bile, and pancreatic juice to determine the pattern of distribution and the relative degree of biliary and pancreatic excretion.

Six mongrel dogs weighing 15 to 20 kg each were used. General anesthesia was induced by giving ketamine hydrochloride (88 mg/kg of body weight) plus xylazine (13 mg/kg). Additional doses were given as required to maintain anesthesia for the period of the experiment. A Harvard ventilator and endotracheal incubation were used to maintain respiration on room air.

Laparotomy was performed, the second part of the duodenum was opened, and the main pancreatic duct was cannulated with fine polyethylene tubing. The accessory pancreatic duct was ligated. The common bile duct was opened, and a polyethylene cannula was passed towards the liver and tied in position after ligation of the lower end of the bile duct. The cystic duct was then ligated to exclude the gallbladder and permit collection of hepatic bile. A cannula was placed in a large vein in the foreleg to infuse secretin (0.06 U/kg per min; KabiVitrum) combined with the octapeptide of cholecystokinin (0.004 μg/kg per min; Squibb). Pancreatic juice was collected every 10 min until a constant flow was maintained for 30 min. Base-line samples of pancreatic juice and bile were then collected for 10 min, and a blood sample was taken at the midpoint of the 10-min collection period. Simultaneously, tissue samples of the liver, pancreas, rectus abdominus muscle, and extraperitoneal fat were taken for tissue assays of cefamandole. Cefamandole was then infused in a dose of 50 mg/kg given over a period of 10 min. Samples of blood, bile, pancreatic juice, liver, pancreas, muscle, and fat were taken again at 20, 40, 60, 90, and 120 min after administration of cefamandole.

The samples were assayed by Lilly Research Laboratories by using a microbiological agar diffusion assay with Bacillus subtilis ATCC 6633 as the test microorganism. The cefamandole standard curve levels ranged from 0.25 to 10.0 μg/ml.

Control dog sera were used to dilute serum samples and standard solutions of cefamandole. Bile and pancreatic juice were diluted with phosphate buffer at pH 6.0 and assayed against standard curves of fluids diluted with the buffer. Tissue samples (fat, muscle, liver, and pancreas) were minced and homogenized in the buffer at a ratio of 1 g/10 ml with a Polytron homogenator set at position 7 for 20 s. After centrifugation, the supernatant was assayed for cefamandole activity. The assays of the standards and samples had a relative standard deviation of 10%. The control dog sera and the buffer diluents were tested to ensure that they contained no biological activity. The antibiotic values for the same tissue or fluid were compared statistically by one-way analysis of variance. The values for different tissues or fluids at the same collection time were compared by one-way analysis of variance and the Student-Neuman-Keuls test.

The mean concentrations of cefamandole after intrave-

FIG. 1. Semi-log plot of mean levels of cefamandole in body fluids and tissues after a 50-mg/kg intravenous dose.

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nous injection of 50 mg/kg are shown in Fig. 1. The highest concentrations were usually achieved in 20 min, and they slowly declined over the 2-hour period of the study. The levels in bile were considerably higher than those in serum, whereas the levels in pancreatic juice were very low. Table 1 shows the mean concentrations ± standard errors of the means of levels in body fluids and tissues. The concentration in bile was statistically greater than the concentration in serum at all times and exceeded the level in serum by a factor of 15 to 20. In contrast, the levels in pancreatic juice were always statistically less than those in serum and were virtually undetectable after 40 min. For tissues, the highest values were observed in the liver, with statistically lower values in the pancreas and still lower values in muscle and fat. The means of the highest concentrations of cefamandole measured in fluids and tissues are compared in Table 2, in which the level in serum is taken as 100%. The concentration in bile was 20 times the level in serum and 30 times the concentration in liver. In contrast, the levels in pancreatic juice reached only 4% of the level in serum and 14% of the level in pancreatic tissue.

Cefamandole has been shown in previous studies to be excreted at high concentrations in hepatic bile (6, 9). Some authors have considered these levels to be of value in the prophylaxis and therapy of hepatobiliary infections (4, 8, 11). Our work confirms the presence of high biliary levels of cefamandole greatly exceeding the levels in serum. The difference was often 15- to 20-fold. This implies active secretion by hepatocytes and indicates that cefamandole is steadily secreted into the gastrointestinal tract in the bile following intravenous injection. We found that the levels of cefamandole in liver were similar to the corresponding levels in serum, suggesting passive transfer of the drug into the liver. Active transfer must therefore occur between the liver parenchyma and the canaliculus against a high gradient.

In this study, levels in pancreatic juice were low or undetectable. Despite these low levels, the levels in pancreatic tissue were 7 to 20 times higher. These data confirm the presence of a barrier to pancreatic excretion of cefamandole by the acinar cells. In a previous study with conscious dogs, our results suggested the existence of a barrier in the pancreas for certain antibiotics but not for others (3). We were unable to determine whether the barrier occurred at the acinar cell-ductal membrane level or at the blood-acinar cell level. The present study indicates that for cefamandole, the barrier occurs between the pancreatic tissue and the pancreatic juice, that is, at the acinar cell-ductal membrane level.

In our study, secretion and cholecystokinin were used to stimulate the flow of pancreatic juice and bile because of the difficulty in collecting basal pancreatic secretion, which is of very low volume in the anesthetized dog. It is conceivable that the hormones altered excretion of the antibiotic. However, even without hormonal stimulation, biliary cefamandole levels are high (1, 5, 9, 11). The volume of pancreatic secretion obtained by the hormonal infusion was similar to that observed by us following meal meal stimulation and probably corresponds to physiological levels (2).

Levels in pancreatic tissue were approximately 1,500 times the levels in liver but exceeded the corresponding values in muscle and fat. All the levels in tissue appeared to be within the therapeutic range for susceptible organisms. During pancreatobiliary infections, there may be alterations in the levels in tissue related to changes in blood flow and damage to cellular membranes (10), but we have not yet studied these aspects.

TABLE 1. Cefamandole concentrations in fluids and tissues after an intravenous dose

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Serum (μg/ml)</th>
<th>Pancreatic juice (μg/ml)</th>
<th>Bile (μg/ml)</th>
<th>Liver (μg/g)</th>
<th>Pancreas (μg/g)</th>
<th>Muscle (μg/g)</th>
<th>Fat (μg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.3</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;1.0</td>
<td>101.4 ± 13.3d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>160 ± 22b,c</td>
<td>6.6 ± 1.5d</td>
<td>2.86 ± 574c</td>
<td>101.4 ± 13.3d</td>
<td>44.0 ± 4.4e</td>
<td>20.5 ± 3.4d,e</td>
<td>9.0 ± 1.7d,e</td>
</tr>
<tr>
<td>40</td>
<td>70 ± 11b,c</td>
<td>1.7 ± 0.7e</td>
<td>3.07 ± 493c</td>
<td>74.5 ± 14.0d</td>
<td>25.9 ± 2.5e</td>
<td>16.3 ± 2.1e</td>
<td>13.8 ± 4.0e</td>
</tr>
<tr>
<td>60</td>
<td>48 ± 7b,c</td>
<td>1.0 ± 0.3e</td>
<td>1.84 ± 248c</td>
<td>41.0 ± 3.3d</td>
<td>20.4 ± 4.0e</td>
<td>14.2 ± 3.6e</td>
<td>9.7 ± 4.0e</td>
</tr>
<tr>
<td>90</td>
<td>27 ± 5b,c</td>
<td>0.6 ± 0.4e</td>
<td>8.01 ± 168c</td>
<td>15.8 ± 1.3</td>
<td>10.6 ± 3.9</td>
<td>6.9 ± 1.0</td>
<td>3.9 ± 0.7e</td>
</tr>
<tr>
<td>120</td>
<td>17 ± 4b,c</td>
<td>&lt;0.5f</td>
<td>2.77 ± 33c</td>
<td>7.8 ± 1.1</td>
<td>5.4 ± 1.7</td>
<td>6.7 ± 1.9</td>
<td>4.4 ± 1.1</td>
</tr>
</tbody>
</table>

" Mean ± standard error of the mean; n = 6.  
* P < 0.05 compared with bile.  
* P < 0.05 compared with value for pancreatic juice.  
* P < 0.05 compared with value for pancreas.  
* P < 0.05 compared with value for liver.

TABLE 2. Highest cefamandole levels observed as percentages of highest level in serum

<table>
<thead>
<tr>
<th>Fluid or tissue</th>
<th>Highest level (μg/ml)</th>
<th>% of level in serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>160 ± 22c</td>
<td>100</td>
</tr>
<tr>
<td>Bile</td>
<td>3,071 ± 574c</td>
<td>1,931</td>
</tr>
<tr>
<td>Liver</td>
<td>101 ± 14c</td>
<td>64</td>
</tr>
<tr>
<td>Pancreas</td>
<td>44 ± 12c</td>
<td>28</td>
</tr>
<tr>
<td>Muscle</td>
<td>20 ± 12c</td>
<td>13</td>
</tr>
<tr>
<td>Fat</td>
<td>14 ± 12c</td>
<td>9</td>
</tr>
<tr>
<td>Pancreatic juice</td>
<td>7 ± 12c</td>
<td>4</td>
</tr>
</tbody>
</table>

LITERATURE CITED