Excretion of Cephalothin and Cefamandole by the Normal Pancreas and in Acute Pancreatitis in Dogs

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Nine mongrel dogs were studied to evaluate the excretion of cefamandole (five dogs) and cephalothin (four dogs) in the pancreatic fluid. Each dog was studied before and after the induction of pancreatitis, with 2 weeks between studies. After intravenous administration of a 25-mg/kg dose of either cephalosporin, serum and pancreatic fluid concentrations were monitored for 6 h. Both cephalothin and cefamandole were excreted in bactericidal concentrations in the normal pancreas and in acute pancreatitis. Clearance of cefamandole (290 ml/min) and cephalothin (348 ml/min) were similar pre- and postinduction of pancreatitis. Serum albumin concentration was less during the post-pancreatitis phase compared with the pre-pancreatitis phase. Penetration of cephalothin was reduced in pancreatitis, whereas cefamandole penetration increased in pancreatitis.

The usefulness of antibiotics in acute pancreatitis is controversial (6, 8–10). To assess the ability of an antibiotic to prevent serious infectious complications, such as a pancreatic abscess, it is important for it to be bactericidal against the organisms usually associated with the condition. In addition, the antibiotic must be able to penetrate the gland so that it can act against the bacteria.

Recently we showed that tobramycin penetrates the pancreas in bactericidal concentrations both in the normal gland and in acute pancreatitis in dogs (11). By considering the usual bacteria isolated in pancreatic abscesses (1–5, 7), it was suggested that improved bactericidal activity or synergy might be achieved by combining tobramycin with a cephalosporin, provided that the cephalosporin was also excreted in the pancreatic secretion. This study therefore examines the excretion of two representative cephalosporins, cefamandole and cephalothin, both in the normal gland and in acute pancreatitis in dogs.

**MATERIALS AND METHODS**

**Animal Model.** This study measured the antibiotic concentrations in pancreatic secretions collected from pancreatic fistulae over a 6-h period. Pancreatitis was induced into each dog, and each dog was studied 15 days later. Eleven mongrel dogs were allocated to one of two groups. Six, ranging from 21.5 to 26.2 kg, were given cefamandole, and five, ranging from 17.4 to 22.0 kg, were given cephalothin.

The experiment was conducted as previously described (11). The experimental period was 15 days. On day 1, pancreatic fistulae were designed (J. G. N. Studley, A. Faichney, and W. G. Schenk, Jr., Surg. Gynecol. Obstet., in press). On day 2, dogs were placed in a Pavlov frame for pharmacokinetic study. A long line was introduced into the inferior vena cava via a hind leg vein for blood sampling. A control sample of pancreatic fluid was collected over a 15-min period, and a control blood sample was also taken. Cefamandole or cephalothin (25 mg/kg) was then injected into a foreleg vein. Pancreatic juice was collected over 15-min periods for 1 h, 30-min periods for 1 h, and 1-h periods for 4 h. Blood samples were taken at the end of each collection period. An additional sample was taken for serum protein estimation. On day 14, acute pancreatitis was induced, and on day 15, cephalosporin pharmacokinetics were studied again. All of the dogs were then sacrificed, and sections of the pancreas were taken for histological examination.

**Pharmacokinetic analysis.** Concentrations of cephalosporin in the serum and in the pancreatic fluid were determined by biological assay, using standards made in the fluid being quantitated. The amount of drug in each pancreatic fluid sample was calculated by multiplying the concentration by the volume. The pancreatic fluid excretion rate was determined by dividing the amount in each collection by the time of collection. The serum area under the curve (AUC) and the pancreatic AUC were determined by the trapezoidal rule, and clearance was calculated as dose divided by AUC. The penetration ratio for pancreatic fluid was the pancreatic fluid AUC divided by the serum AUC. All data were expressed as mean ± standard deviation, and statistical testing was done, using the unpaired t test.

**RESULTS**

One dog was rejected from each group; one died after the first operation from a leak around the fistula, and the other developed renal failure.
TABLE 1. Comparison of physiological characteristics and pancreatic fluid penetration for cefamandole and cephalothin in the study dogs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serum creatinine (mg/dl)</th>
<th>Serum albumin (g/dl)</th>
<th>Cephalosporin clearance (ml/min)</th>
<th>Pancreatic fluid-to-serum AUC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-induction</td>
<td>Post-induction</td>
<td>Pre-induction</td>
<td>Post-induction</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>3.1 ± 0.1</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>(n = 4)</td>
<td></td>
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</tr>
<tr>
<td>Cefamandole</td>
<td>0.9 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>3.0 ± 0.3</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>(n = 5)</td>
<td></td>
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</tbody>
</table>

¹ Clearance was calculated as dose ÷ AUC and expressed as milliliters per minute.
² Pancreatic fluid-to-serum AUC ratio was calculated from the pancreatic fluid AUC ÷ serum AUC.
³ Not significant (P = 0.08).

after the second operation, leaving five dogs in the cefamandole group and four dogs in the cephalothin group. All of the dogs had stable renal function (Table 1), and all had a lower serum albumin concentration after induction of pancreatitis, as shown in Table 1. Histology of the pancreas confirmed acute focal pancreatitis in all of the dogs.

The mean volumes of pancreatic juice secreted per hour in the pre-pancreatitis phase of the experiment were 11.42 ± 2.66 ml in the cefamandole group and 11.76 ± 1.99 ml in the cephalothin group. In the post-pancreatitis phase, the mean volumes were 9.96 ± 2.12 ml in the cefamandole group and 6.87 ± 2.02 ml in the cephalothin group.

Cephalosporin pharmacokinetics. Neither cephalosporin showed a significant change in clearance pre- to post-pancreatitis. Peak concentrations in pancreatic fluid were between 2.0 and 12.0 for cefamandole and between 1.0 and 8.0 for cephalothin. The volumes of pancreatic secretion showed considerable fluctuation during the short collection periods. We therefore expressed the data as an excretion rate in pancreatic fluid for pharmacokinetic analysis. Serum concentrations (micrograms per milliliter) and pancreatic fluid excretion rates (micrograms per hour) were expressed as the mean ± standard deviation for all nine dogs and are plotted versus time in Fig. 1 and 2. Cephalothin serum concentrations and pancreatic fluid excretion rates were similar in the two phases of the experiment (Fig. 2), whereas serum concentrations and pancreatic fluid excretion rates of cefamandole were visibly greater in the post-pancreatitis phase compared with the pre-pancreatitis phase (Fig. 1). Relative penetration by each cephalosporin is given in Table 1. It can be seen that cephalothin penetrates the normal gland to a greater degree than cefamandole does, and cefamandole penetration is greater in acute pancreatitis. Neither of these conclusions were made from sufficient observations to achieve statistical significance, although the cefamandole relationship, at P = 0.08, was much closer to statistical significance than the other trends noted in this study.

FIG. 1. Mean ± standard deviations of cefamandole serum concentrations and pancreatic fluid excretion rates (PFER) over 6 h. Values are shown for the identical body weight-related dosage given both pre- and post-pancreatitis. Pancreatic fluid concentrations fell below assay sensitivity (0.25 µg/ml) at 3 h after the dose.
DISCUSSION

The ability of antibiotics to penetrate the pancreas in acute pancreatitis is largely unknown. The cephalosporins that we studied were excreted in the pancreatic fluid in bacterial concentrations, but the two drugs studied appeared to differ in their ability to penetrate the pancreas. Cefalothin penetration was greater in the normal pancreas, and cefamandole penetration was greater in bile-induced pancreatitis (Table 1).

It is not clear why cefamandole concentrations and pancreatic fluid penetration should be greater in acute pancreatitis than in the normal gland, but there are several possibilities. The serum albumin concentration was lower in the post-pancreatitis phase. In serum, cefamandole is 75% protein bound versus 20% for cefalothin. Thus, more free cefamandole would be available for diffusion into the tissues, and more would be excreted in pancreatic fluid. The effect of free fraction would also occur with cefalothin, but the effect of hypoproteinemia is much less pronounced on drugs with low protein binding such as cefalothin.

The data also argue against a penetration change due to altered serum kinetics by renal or liver disease, since clearance and renal functions showed no significant changes pre- to post-pancreatitis. Furthermore, the AUC ratio expression we used removes the influence of increased or decreased serum excretion.

A third possibility for different penetration is molecular differences between cefamandole and cefalothin. Compared with cefalothin, cefamandole is excreted in far greater amounts in bile, as well as in pancreatic fluids. Therefore, the differences observed in pancreatic fluid excretion may be related to the greater lipophilicity of cefamandole, as opposed to that of cefalothin.

There is no general agreement on the place for antibiotics in the treatment of pancreatitis and almost no data on the penetration of this organ by antibiotics of current choice. This study shows that cephalosporins may penetrate into the fluid secretions produced by focal acute pancreatitis. We do not know whether penetration would remain adequate in more severe cases of pancreatitis. However, since many patients with acute pancreatitis suffer from chronic alcohol abuse, malnutrition, and liver disease and are often hypoproteinemic, our data suggest that greater amounts of cefamandole might be excreted in the pancreatic fluid, as occurred in these dogs.

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LITERATURE CITED