Pancreatic concentrations of cefepime

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The concentrations of cefepime in pancreatic pseudocyst fluid ($n = 4$), pancreatic tissue ($n = 4$) and pancreatic fistula fluid ($n = 1$), and simultaneous plasma concentrations, were measured after intravenous administration of a single 2 g dose to nine patients. Mean plasma concentration was 27.4 mg/L between 120 and 200 min after the end of infusion. Mean pancreatic cefepime concentration was 6.3 mg/L in pseudocyst and 10.7 mg/L in pancreatic tissue. Cefepime was detected by 30 min after the end of the perfusion in pancreatic fistulae fluid, and persisted at 8 h. We conclude that cefepime is a potentially useful antibiotic in prevention and treatment of pancreatic infection.

Introduction

Antibiotic tissue penetration into human pancreas is a major criterion of efficacy during pancreatic infections, particularly in acute pancreatitis (AP). Cefepime (Axepim) is a fourth-generation synthetic cephalosporin active against the bacteria\textsuperscript{1} often involved in pancreatic infections.\textsuperscript{2} Cefepime has a good tissue and biological fluid distribution (urine, bile, peritoneal fluid, bronchial mucosa).

The spectrum of activity of cefepime indicates a potential use in the treatment of pancreatic infection, but the concentrations reached in the pancreas are unknown. The objective of this study was to evaluate pancreatic cefepime concentrations.

Patients and methods

Patients

Nine patients were included in this study (seven male, two female; 23–70 years old). Four patients suffered from pancreatic pseudocyst (retention cyst in two cases and necrotic in two cases) requiring aspiration (patients P1–P4). Four patients suffered from a pancreatic lesion requiring surgical resection (patients C1–C4). One patient suffered from a pancreatic pseudocyst treated by aspiration–drainage with a pancreatic secretion flow rate greater than 10 mL/h (pancreatic fistulae) (patient D). Informed consent was obtained from all patients before admission into the study.

Exclusion criteria were: age <18 years, severe liver or renal failure, allergy to cephalosporins and ongoing antibiotic therapy that could not be replaced by cefepime.

Methods

Patients received 2 g of cefepime (Bristol Myers Squibb, Paris la Défense, France) by rapid intravenous infusion over 30 min. The infusion was started 2.5 h before aspiration in group P and before anaesthetic induction in group C. The exact time interval between the end of infusion and collection of the sample was recorded in groups P and C. In group P, a blood sample was drawn before the cefepime infusion and at the time of aspiration. In group C, a piece of pancreatic tissue was taken from a non-neoplastic zone of the operative specimen and sent to the laboratory on ice. One gram of this sample was ground and centrifuged, and the supernatant was collected. In group C, a blood sample was drawn before cefepime infusion and at the time of aspiration. In group C, a piece of pancreatic tissue was taken from a non-neoplastic zone of the operative specimen and sent to the laboratory on ice. One gram of this sample was ground and centrifuged, and the supernatant was collected. In group C, a blood sample was drawn before cefepime infusion and at the time of pancreatic resection. In patient D, a blood sample and a pancreatic fluid sample were collected before the cefepime infusion, then 10 min, 30 min, 1 h, 2 h, 4 h and 8 h after the end of the cefepime infusion. Blood samples were centrifuged and the serum was then frozen. Pancreatic samples were also frozen.

Blood pressure and pulse were monitored for 6 h after aspiration in group P and for 12 h after the start of drainage in patient D. A complete blood count was performed at the...
end of sample collection and the following morning. The usual postoperative surveillance was performed in group C and any unusual events occurring during the 12 h after cefepime infusion were recorded.

Cefepime was assayed in serum and pancreatic secretions by liquid chromatography according to the technique described by Barbhaiya et al.\textsuperscript{3} This technique consists of inverse phase chromatography after deproteinization by a combination of acetonitrile–trichloroacetic acid (for serum) and extraction by dichloromethane with UV detection at 280 nm with a sensitivity of 0.05 FSU. Cefadroxil was used as internal standard.

This protocol was approved by the regional ethics committee.

Results

Surgical intervention was a Whipple procedure in three cases (pancreatic cancer in two cases and bleeding pancreatic duct in one case) and a distal pancreatectomy with splenectomy in one case (pancreatic pseudocyst). Plasma cefepime concentrations before infusion were undetectable in all patients. The time between the start of the infusion and pancreatic tissue and fluid sampling and the plasma and pancreatic cefepime concentrations are indicated in the Table. The time between the start of the infusion and pancreatic sampling ranged from 2 h to 2 h 40 min in group P, and from 2 h 20 min to 3 h 20 min in group C.

The mean plasma cefepime concentration determined between the 120 and 200 min after the end of the infusion was 27.4 mg/L (range: 6.6–46.8 mg/L). The mean pancreatic cefepime concentration in group P was 6.3 mg/L. The mean pancreatic cefepime concentration in group C was 10.7 mg/L. Plasma and pancreatic cefepime concentrations in patient D are shown in the Figure. No complication was observed.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Concentration (mg/L)</th>
<th>Plasma</th>
<th>Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>2 h 30 min</td>
<td>30.8</td>
<td>12.5</td>
</tr>
<tr>
<td>P2</td>
<td>3 h 40 min</td>
<td>6.6</td>
<td>2.1</td>
</tr>
<tr>
<td>P3</td>
<td>2 h</td>
<td>39.5</td>
<td>2.5</td>
</tr>
<tr>
<td>P4</td>
<td>2 h 30 min</td>
<td>11.4</td>
<td>8</td>
</tr>
<tr>
<td>C1</td>
<td>3 h 15 min</td>
<td>27</td>
<td>12.9</td>
</tr>
<tr>
<td>C2</td>
<td>2 h 20 min</td>
<td>31.1</td>
<td>4.8</td>
</tr>
<tr>
<td>C3</td>
<td>3 h 10 min</td>
<td>28</td>
<td>20.9</td>
</tr>
<tr>
<td>C4</td>
<td>3 h 20 min</td>
<td>46.8</td>
<td>4</td>
</tr>
</tbody>
</table>

Discussion

Infection is currently the leading cause of death in AP.\textsuperscript{4} Superinfection of the necrotic and inflammatory tissue in the context of severe AP often occurs early and is caused predominantly by colonic bacteria, primarily \textit{Escherichia coli}, \textit{Staphylococcus}, \textit{Pseudomonas}, \textit{Proteus}, \textit{Klebsiella} and \textit{Enterobacter}.\textsuperscript{2} Good distribution of the antibiotic into pancreatic tissue and pancreatic secretions and efficacy against the bacteria responsible are essential for both prevention and treatment of this superinfection. The pancreatic concentrations of some antibiotics have been determined and the value of some of them in prevention of superinfection of AP has been studied. Previous prospective studies that failed to demonstrate any effect of prophylactic antibiotics in AP used ampicillin as the study drug, an agent now known not to appear at therapeutic concentrations in either pancreatic tissue or pancreatic juice. The most effective antibiotics are ceftazidime, ofloxacin, cipro-
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Floxacin and imipenem. Empirical antibiotic therapy using antibiotics achieving satisfactory pancreatic concentrations decreases the morbidity and mortality of severe pancreatitis.

Cefepime is a fourth-generation cephalosporin with low plasma protein binding and therefore good penetration into interstitial fluid and tissues. Cefepime is resistant to most penicillinases and has a low affinity for β-lactamases. The species usually susceptible to cefepime include E. coli, Proteus vulgaris, Proteus mirabilis, Serratia, Enterobacter and Pseudomonas aeruginosa and Klebsiella pneumoniae are moderately or inconsistently susceptible. Cefepime is active against most of the bacteria responsible for bacterial contamination of pancreatic necrosis during AP, but is not active against Enterococcus or methicillin-resistant Staphylococcus, which in recent studies appear to be increasingly responsible for pancreatic superinfections.

Mean plasma concentrations determined after intravenous infusion of 2 g of cefepime were 44.8 mg/L at 2 h and 19.2 mg/L at 4 h, which correspond to our results (27.4 mg/L between 2 h and 3 h 20 min). After intravenous infusion of 2 g of cefepime, peritoneal, bile and gall bladder cefepime concentrations were 5.7, 15.5 and 5.4 mg/L, respectively, 8 h after infusion, peritoneal and appendicular concentrations were 14.4 and 4.8 mg/L, respectively, 6 h after infusion, and the mean concentration in bronchial mucosa was 24.1 mg/L 5 h after infusion. The concentration in pancreatic secretions and pancreatic tissue was comparable to the concentrations obtained in the appendix or gall bladder and lower than bronchial concentrations. Cefepime was detected in pancreatic secretions by 30 min after the end of the infusion and a concentration >5 mg/L was still present at the 8 h. Previous in vitro studies with cefepime indicate that the MIC₉₀ for pathogens such as E. coli, Proteus, Klebsiella and Enterobacter is usually ≤4 mg/L. Cefepime concentrations in pancreatic secretions and pancreatic tissue were higher than the MICs for the main bacteria responsible for pancreatic infection.

In conclusion, cefepime, with its high pancreatic concentrations, is a potentially useful antibiotic in the prevention and treatment of pancreatic infection.

References


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