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Assesment of Antimicrobial Penetration into the Pancreatic Juice in Dogs

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Summary

The pancreatic ductal penetration of piperacillin, cefuzonam, fosfomycin and netilmicin, injected intravenously, was studied in four dogs with chronic pancreatic fistula. Serum and pancreatic juice were collected simultaneously, frozen, and later assayed for antibiotic concentration. Each antibiotic achieved its therapeutic serum level. The pancreatic ductal levels of piperacillin and cefuzonam were therapeutic, in contrast, the fosfomycin and netilmicin levels were subtherapeutic. These results are considered to be of interest in prevention and treatment of pancreatic infections.

Introduction

In a review of 10,435 cases of endoscopic retrograde cholangiopancreatography (ERCP) Bilbao et al.[1], demonstrated that ERCP can induce pancreatic sepsis in patients with pancreatitis or pancreatic duct obstruction and that retention of contrast medium readily leads to abscess formation in those with pseudocysts of the pancreas.

Considering the risk of infectious complications of ERCP, Davis et al.[2], emphasized the necessity of prophylactic parenteral administration or the incorporation of antibiotics in a contrast medium. There is, furthermore, a consensus about the necessity for systemic administration of antibiotics to prevent secondary following acute pancreatitis.

Although systemic antibiotic therapy, targeted at the organisms associated with diseases of the pancreas, is required in various situations, the penetrance of antibiotics into pancreatic juice has not been sufficiently investigated. Moreover, only a small number of antibiotics have been included in the evaluations to date, and pancreatic ductal penetration of new antibiotics, which have been developed, remains unknown. In this study, we prepared a dog model with chronic pancreatic fistula and studied the antibiotic concentrations in the pure pancreatic juice.

Key words: Pancreatic ductal penetration, Antibiotic concentrations in the pancreatic juice, Minimum inhibitory concentration$_{80}$ (MIC_{80}), Antibiotic therapy, Dog with chronic pancreatic fistula.
索引語　抗生剤膵液移行性，膵液抗生剤濃度，80％発育阻止濃度 (MIC_{80})，抗生剤療法，慢性膵瘻犬.
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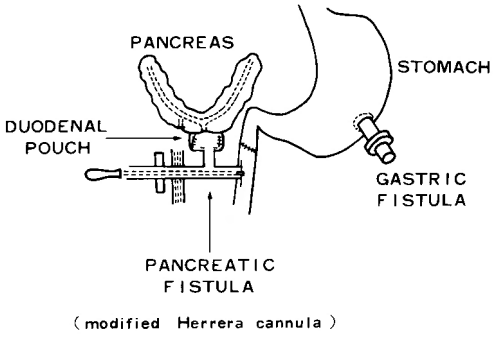

Fig. 1 Operative schema for experimental model.

Materials and Methods

The experimental model is described first. Taking advantage of the anatomical characteristic of the dog that the pancreatic duct and bile duct open in separate duodenal papillae, a chronic pancreatic fistula was constructed using a modified Herrera cannula in 4 adult mongrel dogs of either sex weighing 18–29 Kg according to the method of Hosotani et al.[3] (Fig. 1). A median laparotomy was performed under sodium pentobarbital anesthesia. First, the accessory pancreatic duct was incised and ligated, and a duodenal pouch about 5 cm in lenght constructed at the intact papillary opening of the main pancreatic duct. Reconstruction was made by end-to-end duodenoduodenostomy, and an external pancreatic fistula was created by inserting a modified Herrera cannula between the duodenal pouch and the duodenum. This cannula, which prevented entry of intestinal juice, allowed collection of the pure pancreatic juice through the duodenal pouch for experiments and preserved the physiologic flow of the pancreatic juice into the duodenum during non-study periods. Food and water intake was suspended for 5 days after operation, during which time the animals were maintained by total parenteral nutrition via the external jugular vein. The animals were used for the experiments when the oral dietary intake was returned to the preoperative level or above after a recovery period of at least 3 weeks.

Table 1 Assayed drug combination and dosage

Group	n	Drugs	Dosage
I	4	Cefuzonam (CZON)	1 g
		Fosfomycin (FOM)	1 g
II	4	Piperacillin (PIPC)	1 g
		Netilmicin (NTL)	100 mg

Table 2 Antibiotic levels in serum and pancreatic juice

(μg/ml)

Drug	Serum 5′	Serum 60′	Pancreatic juice 5′	Pancreatic juice 60′
CZON	101.9±19.0	49.4±3.5	4.4±1.0	9.6±4.7
FOM	171.8±22.7	60.9±6.3	4.8±1.9	2.8±1.0
PIPC	184.8±13.1	38.8±3.8	10.6±3.7	14.7±5.6
NTL	24.0±1.1	11.0±0.5	0.2±0.17	0.95±0.34

M±SEM. * $P<0.05$ (as compared to NTL)

Four antibiotics, namely piperacillin (PIPC) of penicillin group, cefuzonam (CZON) of the cephalosporin group, netilmicin (NTL) of the aminoglycoside group, and fosfomycin (FOM), were examined.

According to the method of Sugawa et al.[8], two of these drugs were dissolved in 20 ml physiologic saline and administered simultaneously[9] by intravenous injection in the combinations and doses, (shown in Table 1), over 2 minutes exactly. Peripheral blood and pancreatic juice were collected 5 and 60 minutes after the beginning of the intravenous injection. The season for this is that all of these antibiotics show a peak blood concentration about 5 minutes after intravenous injection and have a half-life in the serum of about 60 minutes[5], and also because a peak biliary concentration can be observed about 60 minutes after injection[10]. Secretin (50 units), was then administered before the antibiotics in order to stimulate external pancreatic secretion. After cold centrifugation, the samples were stored at −20°C until assays. PIPC and CZON were assayed by high performance liquid chromatography[9], NTL by fluorescence immunoassay, and FOM by the test-standard curve method after alkali degradation.

Results

Table 2 shows the serum concentrations of CZON and FOM in group 1 at 5 and 60 minutes. In the pure pancreatic juice, the CZON and FOM concentrations were 4.4±1.0 (M±SEM) and 4.8±1.9 μg/ml, respectively at 5 minutes and 9.6±4.7 and 2.8±1.0 μg/ml, respectively at 5 minutes and 9.6±4.7 and 2.8±1.0 μg/ml, respectively, at 60 minutes.

In group II, the serum concentrations of PIPC and NTL at 5 and 60 minutes are as shown in Table 2. The concentrations in pancreatic juice were 10.6±3.0 and 0.2±0.17 μg/ml for PIPC and NTL at 5 minutes and 14.7±5.6 and 0.95±0.34 μg/ml, respectively, at 60 minutes. Significant differences in the concentrations in pancreatic juice could be observed only between NTL and the other 3 drugs at 5 and 60 minutes ($P<0.05$, Table 2).

Discussion

Study of the penetrance of antibiotics into the pancreatic juice was first done by Howard et al.[4], in 1951. They examined the concentrations of penicillin, sulfadiazine, streptomycin, the aureomycin in a 32-year-old patient with an external pancreatic fistula after a gunshot wound and reported good transport of penicillin and sulfadiazine to pancreatic juice. In the pancreatic juice col-

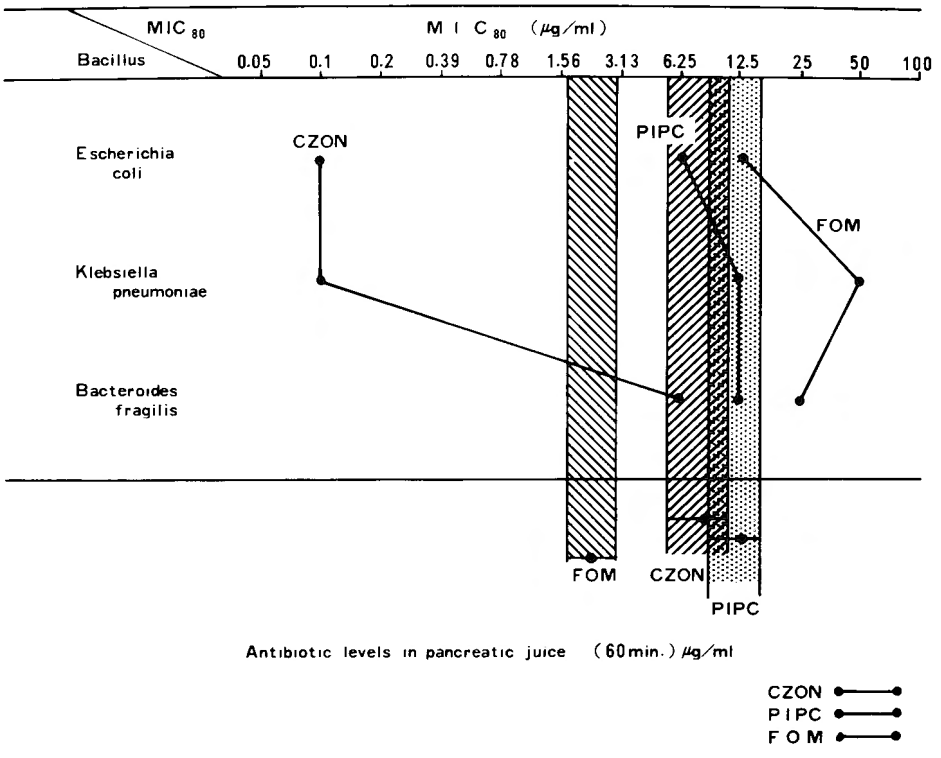

Fig. 2 Correlation of antibiotic levels in pancreatic juice and MIC_{80}.

lected by ERCP, Wallance et al.[12], examined pancreatic ductal penetration of mezlocillin, metronidazole, trimethoprim-sulfamethoxazole concentrations reached therapeutic levels but the penetration of mezlocillin was unsatisfactory. They also stated that the penetrance into pancreatic juice was good for lipophilic drugs such as chloramphenicol, metronidazole, and trimethoprim but poor in water soluble drugs such as β-lactams and aminoglycosides. Furthermore, they suggested that weakly acidic drugs may better penetrate the alkaline pancreas. Sugawa et al.[8], also showed good pancratic penetration of penetration of ampicillin, mezlocillin, cefamandole, gentamicin, and amikacin in ERCP specimens.

Among animal experiments, Rubinstein et al.[7], produced a duodenal fistula in adult mongrel dogs using a modified Thomas cannula and examined penetration of clindamycin into pancreatic secretion. The concentration of this antibiotics in pancreatic juice was 1.32 ± 5.5 μg/ml, which was 4–6% of its serum concentration. Trudel et al.[11], produced hemorrhagic pancreatitis by infusing trypsin and bile into the pancreatic duct of adult mongrel dogs and then studied the tissue concentrations of antibiotics in the normal pancreas and pancreas during pancreatitis. According to their results, the concentrations of clindamycin, metronidazole, and chloramphenicol reached the therapeutic levels in both the normal pancreas and inflammed pancreas while those of gentamicin, cefazolin, and tetracycline did not. On the basis of these findings, they recommended the first drugs in pancreatic infections.

The history of the study of pancreatic ductal penetration of antibiotics has been summarized above. According to our results, the concentration in the pancreatic juice was highest for PIPC at 14.7 ± 5.6 μg/ml, followed by CZON at 9.6 ± 4.7 μg/ml, and FOM at 2.8 ± 1.0 μg/ml. These results were comparable to those of Howard et al.[4] As for aminoglycosides, their penetration into the pancreatic juice was poor as reported by Sugawa et al.[8], as well as Trudel et al.[11] We studied minimum inhibitory concentration (MIC), especially MIC_{80} against clinically isolated bacteria, of PIPC, CZON, and FOM in consideration of their clinical use. MIC_{80} against *Escherichia coli,* which is frequently responsible for intraperitoneal infections, was 6.25, 0.1 and 12.5 μg/ml for PIPC, CZON, and FOM, respectively; that against *Klebsiella pneumoniae* was 12.5, 0.1, and 50.0 μg/ml, respectively; that against *Bacteroides fragilis* was 12.5, 6.25 and 25.0 μg/ml, respectively. Also, in light of the antibacterial potency of each drug, PIPC and CZON are considered to have therapeutic effects (Fig. 2). No significant differences, however, were observed in the concentration of PIPC, CZON, and FOM in the pancreatic juice, and the concentration of NTL alone was significantly different from those of the other three drugs. From these observations, PIPC and CZON appear to be comparable with respect to the penetrance into the pancreatic juice, but further studies with a larger number of samples are needed. Studies with other antibiotics are also in progress. At any rate, the present results hopefully may serve as a future reference in the treatment of pancreatic infections as well as in the development of new drugs.

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和文抄録

抗生剤膵液移行性に関する実験的評価

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膵臓を標的臓器として抗生剤の全身投与を必要とする機会が多々あるにもかかわらず，抗生剤の膵液移行性については，いまだ充分には検索されていない．そこで著者らは，雌雄雑種成犬4頭を用いて慢性膵瘻犬を作製し，各種抗生剤の膵液移行性について実験的に検討した．検討した薬剤は，piperacillin (PIPC), cefuzonam (CZON), netilmicin (NTL), fosfomycin (FOM) の4種の抗生剤である．静注60分後の膵液濃度は，PIPC: 14.7±5.6 μg/ml であり，CZON: 9.6±4.7 μg/ml, FOM: 2.8±1.0 μg/ml, NTL: 0.2±0.17 μg/ml であった．そして，血清濃度との比較，各種薬剤の MIC_{80} との検討により，piperacillin, cefuzonam の膵管内への移行性は優れており，fosfomycin, netilmicin では治療域に達していないと考えられた．これらの結果は，膵臓に関連する感染症の予防および治療に関して興味深いものであると思われた．