Penetration of moxifloxacin into the human pancreas following a single intravenous or oral dose

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Objectives: Failure to prevent secondary infectious complications in acute necrotizing pancreatitis (ANP) is attributable in part to the limited penetration of antimicrobial drugs. As newer quinolones are particularly attractive owing to their antimicrobial activity, for the first time we studied the penetration of moxifloxacin into pancreatic tissue in patients.

Patients and methods: In this prospective, non-comparative clinical trial, 60 patients undergoing elective pancreas resection received a single oral or intravenous (iv) dose of 400 mg moxifloxacin for perioperative antimicrobial prophylaxis. The concentration of moxifloxacin was measured in samples taken from blood and from pancreatic tissue at the beginning and at the end of resection.

Results: Mean moxifloxacin concentrations in pancreatic tissue following iv or oral administration were 3.1 – 0.9 and 2.7 – 1.4 mg/kg at 3–3.7 h post-dose (first sampling) and 3.6 ± 1.5 and 3.1 ± 1.8 mg/kg at 4.3–5.3 h post-dose (second sampling), respectively. Corresponding mean plasma concentrations of moxifloxacin were 1.8 ± 0.5 and 1.2 ± 0.6 mg/L (first sampling) and 1.5 ± 0.4 and 1.0 ± 0.5 mg/L (second sampling), respectively. From first to second sampling, the mean tissue-to-plasma ratios varied from 1.8 – 0.6 to 2.6 – 1.2 (iv) and from 2.4 – 0.8 to 2.4 – 1.2 (oral). Pancreatic tissue concentrations of moxifloxacin exceeded the MIC90 for the relevant pathogens covered by moxifloxacin for at least 5 h after dosing.

Conclusions: Moxifloxacin has been demonstrated to penetrate efficiently into human pancreatic tissue following iv or oral administration. From a pharmacological perspective, moxifloxacin appears to be promising for prophylaxis and treatment of local pancreas infections. Whether it is beneficial in the prevention and therapy of infectious complications in patients with ANP should be investigated in a controlled clinical trial.

Keywords: pancreatitis, pharmacokinetics, fluoroquinolones

Introduction

In patients suffering from acute necrotizing pancreatitis (ANP), prophylaxis with antibiotics is still a matter of debate, not only because of the risk of development of resistance but also because of conflicting results from clinical studies. National and international guidelines for the management of acute pancreatitis and even a recent Cochrane review recommend antimicrobial prophylaxis in patients at risk for secondary infection.1–3 In many unblinded trials and meta-analyses prophylactic antibiotics have indeed been shown to result in a reduction of the infection rate and mortality or an improved clinical course.6,7 The only double-blind and also the largest randomized clinical trial, the so-called ASAP study, failed to show a reduction of infection and hospital mortality by antibiotic prophylaxis in patients with severe acute pancreatitis.8

Possible reasons for failure to reduce pancreatic infection are the timing, as prophylactic treatment has to start early in the course of disease to be effective.9–11 and also a limited penetration of antimicrobial drugs. A sufficient penetration into pancreas tissue is necessary to influence the local infection and is explicitly demanded in most guidelines as a prerequisite for antimicrobials.

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used in ANP patients. The pancreas is a specialized site with regard to drug penetration. Some antibiotics such as aminoglycosides do not penetrate well into this compartment. The number of drugs whose penetration into pancreatic tissue has been studied is limited.

Besides imipenem, the fluoroquinolones ciprofloxacin and ofloxacin are among the antibiotics most often recommended for ANP and have shown the highest penetration rates (tissue/plasma ratio) in animals as well as in patients. However, considering the relative shift from predominantly Gram-negative bacteria towards a higher proportion of infections due to Gram-positive organisms noted in recent years, newer third-generation fluoroquinolones with enhanced Gram-positive activity and more convenient dosing intervals like moxifloxacin would be an attractive option. Besides its activity against a broad-spectrum of Gram-negative and of Gram-positive bacteria, moxifloxacin has anti-anaerobic activity as an additional benefit and exhibits an excellent tissue penetration especially into rat pancreas. But as of yet, no human data were available. We therefore evaluated moxifloxacin penetration into pancreatic tissue following administration of a single dose of 400 mg moxifloxacin in patients undergoing pancreas surgery.

Patients and methods

Study population

The study population of this prospective, two-centre, non-comparative Phase I study consisted of 60 patients who planned to undergo elective pancreas resection for pancreas carcinoma or chronic pancreatitis. Patients below 18 years of age, with hypersensitivity against quinolones, pregnancy, severe liver dysfunction (Child Pugh class C), heart failure with reduced left ventricular ejection fraction, arrhythmia requiring medical treatment or chronic renal insufficiency, among others, were excluded from the study.

The study was approved by the responsible Ethics Committee of the Arztekammer Mecklenburg-Vorpommern (II HV 09/2001) and performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Safety

Besides measuring moxifloxacin concentrations in tissue and plasma as the primary parameter of this study, safety was assessed as a secondary variable. All patients were monitored for adverse events from the preoperative phase until day 7 post-surgery.

Analytical methods

Sample preparation and HPLC analysis using ofloxacin as internal standard were performed by methods that have been cross-validated with the Bayer HealthCare Reference Laboratory (Wuppertal, Germany) according to industry standards. This method was also fully validated for the determination of levofloxacin by interchanging of analyte (S-enantiomer of ofloxacin) and internal standard (moxifloxacin).

Procedures and sampling

Before induction of anaesthesia all patients received a single dose of 400 mg moxifloxacin for perioperative antibiotic prophylaxis, either intravenously (20 patients) or orally (40 patients). In order to investigate time effect on pharmacokinetic parameters surgeons had to take pancreatic tissue samples at the beginning of the operation after proven resectability (first sample) and at the end of pancreas resection (second sample). Samples from peripheral venous blood were withdrawn simultaneously and kept at 4°C until centrifugation (12 min, 1500 g) for no longer than 1 h. Tissue samples were snap-frozen in liquid nitrogen immediately after removal. Plasma and tissue samples were frozen and stored at –80°C until analysis for no longer than 6 weeks. No significant loss of analyte was observed during sample preparation and storage. Tissue samples were homogenized in an ice bath using 0.9% NaCl (1:1, v/s) and an Ultraturrax T25 (IKA-Werke, Staufen, Germany) for 1 min.

HPLC assay

Homogenized tissue samples were diluted with an equal volume of water to bring concentrations into the range of calibrators. One hundred microlitres of serum or 40 μL of homogenate was spiked with 20 μL each of aqueous ofloxacin (final concentration: 200 ng/mL) as internal standard and, in the case of the calibrators, appropriate concentrations (100–2000 ng/mL) of moxifloxacin. Then, 20 μL of 25% trifluoroacetic acid (purity >99.5%) was added, and the mixture was vortexed and centrifuged at 6000 g for 4 min. Eighty microlitres of the supernatant was added to 21 μL of 5.0 M aqueous ammonium acetate, and 20 μL of the mixture was subjected to HPLC/fluorescence analysis. The chromatographic system consisted of a guarded YMC Pro C18 column (particle size: 5 μm, pore diameter: 120 Å, 150 mm length, 2 mm inner diameter) maintained at 20°C, and a gradient mobile phase comprising methanol/1.0 M ammonium acetate/H₂O (10:5:85 v/v/v for component A and 40:5:55 for component B), pumped at a rate of 250 μL/min, with 22% initial B changed to stages of 25% and 32% after 1 and 2 min, respectively. Fluorescence detection was performed at an excitation wavelength of 296 nm and an emission wavelength of 504 nm. The retention times were 4.5 and 12.5 min for ofloxacin and moxifloxacin, respectively. The assay was validated intra- and inter-daily according to standard procedures. The lower limits of quantification were set to 30 ng/mL for plasma and 150 ng/mL for pancreatic tissue homogenates with coefficients of variation and relative errors of <5% and <+1%, and 29% and +9%, respectively. Precision and accuracies of other controls in the medium and upper range of the calibration range were better than ±15%. Recoveries ranged between 80% and 85% based on spiking solution.

Statistics

All data were analysed descriptively. Calculations were performed using the SPSS software release 11.0 (SPSS GmbH, Munich, Germany). Results are presented as means ± SD. As data were distributed normally (Kolmogorov–Smirnov test), means of moxifloxacin concentrations were compared using an unpaired t-test (Student’s t-test). Findings were considered statistically significant if the P value was <0.05.

Results

Of the 60 patients enrolled in the study, 47 were male and 13 were female. Mean age was 55.9 ± 13.3 years (range: 25–80) and mean body weight was 72.8 ± 12.0 kg. Underlying disease was chronic pancreatitis in 28 cases and pancreatic carcinoma in 32 cases. For demographic data of the subgroups with oral or intravenous (iv) administration of moxifloxacin, see Table 1.
From the 60 patients enrolled, 13 patients could not be evaluated. In five of them the pancreas was shown to be non-resectable intraoperatively, whereas in three other patients no or too little pancreatic tissue was harvested owing to a complicated course of surgery. In the remaining five cases there were protocol violations, mainly due to failures in sampling.

As shown in other studies, the resectability rate for cancer of the head of the pancreas is ~75–80%. This was also true for this study.

Moxifloxacin was well tolerated; no serious drug reactions were observed. None of the patients had to be excluded because of adverse events.

**iv subgroup**

In the iv subgroup, samples were collected at a mean time of 3.0 ± 0.6 h (first) and 4.3 ± 1.3 h (second) after iv administration of moxifloxacin. Owing to the reasons mentioned above, at the first and the second time-point moxifloxacin tissue concentrations were available from 5 (25%) and 16 (80%) patients, respectively, and plasma concentrations from 8 (40%) and 18 (90%) patients.

Following iv administration of moxifloxacin, mean concentrations were 1.8 ± 0.5 mg/L in plasma and 3.1 ± 0.9 mg/kg in tissue at the first sampling time and 1.5 ± 0.4 mg/L (plasma) and 3.6 ± 1.5 mg/kg (tissue) at the second sampling at the end of pancreas resection (Figure 1). The corresponding penetration rates were 1.8 ± 0.6 and 2.6 ± 1.2 (Figure 2).

**Oral subgroup**

In two patients of the oral subgroup moxifloxacin was administered through a feeding tube; the other patients received moxifloxacin in tablet form. Mean times for first and second sampling were 3.7 ± 0.9 h and 5.3 ± 1.5 h after oral administration of moxifloxacin, respectively. Tissue concentrations were available from 18 (45%) patients at the first and 30 (75%) patients at the second time-point. Plasma concentrations could be obtained from 21 (53%) and 32 (80%) patients, respectively.

Mean concentrations of moxifloxacin after oral administration were 1.2 ± 0.6 mg/L in plasma and 2.7 ± 1.4 mg/kg in pancreatic tissue at the first sampling time and 1.0 ± 0.5 mg/L (plasma) and 3.1 ± 1.8 mg/kg (tissue) at the second sampling (Figure 3). The resulting tissue/plasma ratios were 2.4 ± 0.8 and 3.1 ± 1.2, respectively (Figure 2).

The difference between mean moxifloxacin plasma concentrations following iv versus oral administration was significant at both first and second sampling time-point. Corresponding moxifloxacin tissue concentrations did not differ significantly.

In patients with pancreatic disease the moxifloxacin concentrations found in pancreatic tissue after either iv or oral administration of a single dose of 400 mg moxifloxacin exceeded the MIC90 for the pathogens \(^\text{12}\) most commonly found in infected necroses of patients with severe acute pancreatitis, i.e. *Escherichia coli* (0.008–0.06 mg/L), \(^{22,23}\) methicillin-susceptible *Staphylococcus aureus* (0.06–0.12 mg/L), \(^{22,23}\) *Staphylococcus epidermidis* (0.12–0.25 mg/L), \(^{22,23}\) *Klebsiella* spp. (0.13 mg/L), \(^{23}\) *Enterococcus faecalis* (0.25–0.5 mg/L), \(^{25,26}\) *Bacteroides fragilis* (0.5–1.0 mg/L) \(^{18,23,26}\) and *Enterobacter* spp. (0.06 mg/L), \(^{22,24}\) for at least 5 h after dosing.

### Discussion

In the present study, the penetration ability of moxifloxacin in human pancreatic tissue was evaluated for the first time. These results show that moxifloxacin readily penetrates into human pancreas and achieves high tissue concentrations following a single oral or iv dose. At both sampling times, moxifloxacin concentrations in pancreatic tissue were noticeably higher than the corresponding plasma concentrations. The resulting tissue/plasma ratios varied between 1.8 and 3.1.

While moxifloxacin plasma concentrations exhibited the expected decrease from first (3.0–3.7 h) to second (4.3–5.3 h) sampling time, in pancreatic tissue moxifloxacin concentrations increased from first to second sampling in both the oral subgroup and the iv subgroup. This contrasts with the penetration kinetics in rats, where we observed a sharp and steady decrease of moxifloxacin concentrations in healthy and inflamed pancreatic tissue within 10–240 min after drug administration. \(^{20}\) This
The difference could be explained mainly by the more rapid moxifloxacin metabolism and excretion in rats in comparison with man. Furthermore, possible differences between the acute model in the rat versus the chronic disease in the study patients have to be taken into account. Apart from that, our results are in line with prior findings of a good penetration of moxifloxacin into the pancreas of rats. The pancreatic tissue/plasma ratio of moxifloxacin now found in patients is in the same range as in healthy rats (2) or in rats with experimental ANP (2–3). The high variability can in part be explained by varying sampling. For pefloxacin that has a similar half-life as moxifloxacin, no significant accumulation was observed following multiple-dose administration.

Considering the relative shift of the bacterial spectrum in ANP patients to more Gram-positive pathogens, moxifloxacin is of particular interest as it retains most of the Gram-negative activity of older fluoroquinolones like ciprofloxacin but exhibits a higher Gram-positive activity. Even after a single dose of 400 mg, moxifloxacin tissue concentrations in human pancreas were above the MICs for the most common Gram-negative and Gram-positive pathogens.

Since we could not measure moxifloxacin concentrations over the total 24 h post-dosing, we did not calculate the pharmaco-dynamic index AUC/MIC that is currently used to predict the clinical efficacy of fluoroquinolones.

In comparison with ciprofloxacin, moxifloxacin has weaker in vitro activity against Pseudomonas aeruginosa. Whether this fact is clinically relevant for the prevention of secondary infection of the necrotic pancreas in severe acute pancreatitis has to be evaluated in clinical trials.

The combination with an additional anti-anaerobic drug like metronidazole, as recommended with the use of ciprofloxacin and ofloxacin, might become unnecessary with moxifloxacin because of its anti-anaerobic activity.

In this study, moxifloxacin mean plasma concentrations, especially after oral administration, were somewhat lower than those reported from healthy subjects at corresponding sample times. An explanation for this difference could be a diminished or delayed intestinal absorption before and during surgery due to these patients’ condition, or due to a gastroparesis in the third of patients in the oral subgroup who had diabetes mellitus as underlying disease.
With a total number of 47 patients evaluated, the present study includes the largest ever sample of patients evaluated for pancreas tissue pharmacokinetics of a single antimicrobial. Even in the study by Büchler et al.12 including 89 patients the largest sample per single drug was 15.

A limitation of this study is that the patients enrolled did suffer from pancreas cancer or chronic pancreatitis but not from ANP though that is the actual target population for antibiotic treatment and prophylaxis. In contrast to earlier trials pharmacokinetic studies in patients with acute pancreatitis are no longer feasible as this condition is rarely operated on nowadays and the intervention is restricted to a strict necrosectomy sparing any viable tissue.

However, animal studies indicate sufficient penetration of fluoroquinolones into inflamed pancreas. In a rat-model of ANP Spicak et al.13 have shown that the penetration of β-lactam antibiotics and ofloxacin into pancreatic tissue is not influenced by necrotic inflammation at an early stage of disease. In our olive-oil pancreatitis model we found a 50% higher moxifloxacin concentration in inflamed pancreas than in healthy pancreas tissue.20 From their studies with pefloxacin Bassi et al.28 concluded that antibiotics capable of penetrating into the pancreas under physiological conditions maintain this ability in the course of acute disease with a necrotic component.

Conclusions
Simultaneous measurement of pancreatic tissue and plasma concentrations have demonstrated that moxifloxacin readily penetrates into human pancreatic tissue following iv or oral administration. The resulting tissue concentrations exceed the corresponding plasma concentrations as well as the MICs for the relevant pathogens present in pancreatitis.

Moxifloxacin fulfils the pharmacological requirements to be beneficial for prophylaxis and treatment of local pancreas infections. A controlled clinical trial is warranted for its evaluation in the prevention and therapy of infective complications in patients suffering from ANP.

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