Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients

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Objectives: To assess the pharmacokinetics of moxifloxacin in morbidly obese patients.

Methods: Twelve morbidly obese patients (2 male/10 female, age 25–61 years, weight 98–166 kg, body mass index 43.0–58.2 kg/m²) scheduled for gastric bypass surgery were treated with 400 mg of moxifloxacin orally once daily for 3 days and with 400 mg of moxifloxacin intravenously on day 4 (day of surgery). Pharmacokinetic analysis was performed on day 1 and day 4. Specimens of small intestine, greater omentum and subcutaneous adipose tissue were collected intraoperatively 1.8–3.7 h after moxifloxacin infusion. Moxifloxacin concentrations were determined by HPLC.

Results: The plasma pharmacokinetics (mean ± SD) was comparable to historical data in normal-weight subjects. Oral bioavailability was 79.6±11.5%. After intravenous administration, plasma clearance was 9.6±2.0 L/h, volume of distribution was 165±30 L and area under the curve was 43.7±11.8 mg.h/L. Linear regression analysis showed the volume of distribution to be better correlated with ideal body weight, lean body weight, fat-free mass or height (R² = 0.60–0.67, P = 0.001–0.003) than with total body weight (R² = 0.46, P = 0.015). Whereas mean tissue concentrations in small intestine (6.99±2.34 mg/kg) were twice the concomitant plasma concentrations, the concentrations in greater omentum (0.801±0.168 mg/kg) or subcutaneous fat (0.638±0.180 mg/kg) were only one-quarter of those.

Conclusions: The pharmacokinetics of moxifloxacin is not significantly affected by morbid obesity. No dose adjustment seems to be necessary in this particular population.

Keywords: fluoroquinolones, volume of distribution, size descriptor, HPLC

Introduction

The rise in worldwide obesity, coupled with its associated co-morbidities, suggests that clinicians will encounter obese patients with increasing frequency in their daily practice. Unfortunately, obese subjects are often excluded from clinical trials during the drug development process. As a result, information regarding the impact of obesity on the pharmacokinetics and pharmacodynamics of the majority of drugs remains limited.1 Whereas the absorption of drugs does not appear to be significantly modified in the presence of obesity, physiological changes in obesity can alter both the volume of distribution (V) and the clearance (CL). However, only few studies have been published assessing the effects of obesity on antimicrobial pharmacokinetics. Mostly, the published data refer to antibiotics that historically have included clinical therapeutic drug monitoring, such as aminoglycosides and vancomycin or the widely used β-lactams. Whereas increased V and CL have been observed in these hydrophilic drugs, variable results have been reported with the more lipophilic fluoroquinolones, such as ciprofloxacin, trovafloxacin or garenoxacin.2 The aim of this study was to determine the pharmacokinetics of moxifloxacin in the plasma and adipose tissue of morbidly obese patients undergoing gastric bypass surgery, and to characterize the influence of morbid obesity on the pharmacokinetics of moxifloxacin following oral and intravenous administration.

Patients and methods

Study design and protocol

This was an open-label, non-randomized, monocentric pharmacokinetic study with sequential oral/intravenous treatment over 4 days in patients.
The study (EudraCT No. 2009-014938-15) was conducted in compliance with the Declaration of Helsinki, and was approved by the Ethics Committee at the University of Erlangen. Written informed consent was obtained from all patients.

Thirteen morbidly obese patients with a body mass index (BMI) >40 kg/m² scheduled for gastric bypass surgery (Roux-en-Y gastric bypass, pouch 15 mL, alimentary limb 150 cm) were recruited to the study. One patient was withdrawn after the first administration of moxifloxacin, because of a non-drug-related adverse event during a diagnostic intervention. Prior to surgery, fat-free mass (FFM) was determined using a Tanita BC 420 P MA body composition analyser (Tanita Online, Munich, Germany). The patients were treated with 400 mg of moxifloxacin orally once daily for 3 days and with 400 mg of moxifloxacin intravenously on day 4 (day of surgery). To determine the plasma concentration–time course of moxifloxacin, blood samples were taken as follows: day 1—pre-dose, and after 1, 2, 3, 4, 6, 8, 12 and 24 h or just prior to next dosing; and day 4—pre-dose, and after 1 (end of infusion), 2, 3, 4, 6, 8, 12, 24, 36 and 48 h. One additional plasma sample, obtained after 72–120 h for clinical laboratory testing, was also analysed for moxifloxacin. Specimens of small intestine, greater omentum and subcutaneous adipose tissue were collected intraoperatively 1.8–3.7 h after the administration of moxifloxacin.

All samples were stored at −20°C until analysis. Moxifloxacin was determined in the plasma and tissue homogenate by reversed-phase HPLC and fluorimetric detection, as previously described. Prior to injection onto the analytical column, the plasma was deproteinized with methanol and the tissue was homogenized in methanol/aqueous perchloric acid using an Ultra-Turrax TP 18-10 disperser (IKA-Werke, Staufen, Germany). Gatifloxacin was used as an internal standard. The lower limit of quantification was 0.020 mg/L in the plasma and 0.10 mg/kg in the tissue. Intra- and interassay imprecision and bias, calculated from co-analysed quality control samples in spiked plasma or tissue, were <5%. Most tissue specimens were analysed in duplicate. The intra-assay variation was 11.5% in the fat and greater omentum, and 7.7% in the small intestine, indicating a greater inhomogeneity of these specimens compared with tissue controls.

Safety assessments included the documentation of adverse events, clinical laboratory testing, electrocardiograms and physical examination before dosing and before discharge from hospital.

Pharmacokinetic analysis and statistics
All pharmacokinetic calculations were performed by standard non-compartmental analysis using WinNonlin 6.1 (Pharsight, St Louis, MO, USA). The elimination rate constant \( \lambda_e \) was determined by log-linear regression in the elimination phase, which was identified by visual inspection and covered typically the last 4 or 5 measurements (4 h onwards on day 1 or 8–12 h onwards on day 4). The linear trapezoidal rule was used for calculation of the AUC. For analysis of day 4 measurements, the measured concentrations were corrected for the residual concentrations of the precedent doses using the following formula: 
\[
C_{\text{corrected}} = C_{\text{measured}} - C_{0,\text{day4}} \cdot e^{(-t \cdot \lambda_e)}.
\]
This correction allows the analysis of the plasma concentration–time course as a first dose and, thus, direct comparison with day 1 data.

For day 4, CL and V (=CL/\( \lambda_e \)) were calculated as secondary parameters. Correlations between CL or V with biometric parameters, such as height, total body weight (TBW), lean body weight (LBW), Devine’s estimation of ideal body weight \([\text{IBW} = 45.4 + 0.89 \times \text{height} - 152.4] + 4.5 \text{ (if male)}) and FFM, were calculated by linear regression analysis.

The modified formula \([\text{LBW}_{2005} = (9270 + \text{TBW})/(6680 + 216 \times \text{BMI})]\) for males and \([\text{LBW}_{2005} = (9270 + \text{TBW})/(8780 + 244 \times \text{BMI})]\) for females) for LBW was used, as proposed by Han et al., because the originally developed formula provides paradoxical results for morbidly obese patients. Descriptive statistics, such as mean, SD, median and range, were used as appropriate. \( P<0.05 \) was considered statistically significant. All statistics were calculated with PASW 18 for Mac (IBM Corporation, Somer, NY, USA).

Results
The study medication was well tolerated, no serious adverse events were reported and no drug-related adverse reaction occurred. Also, no clinically relevant changes in laboratory and electrocardiogram parameters (particularly no QT-interval extension) were recorded. One patient experienced an adverse event (retrosternal pain) during pre-operative routine gastroscopy prior to first administration of moxifloxacin. Angiography ruled out coronary disease, but the surgery was postponed and the patient dropped out after the first dose of moxifloxacin. Twelve patients completed the study (Table 1). The study population was representative for patients undergoing bariatric intervention in Germany with regard to age, BMI and sex distribution.

The mean plasma concentration–time course of moxifloxacin following oral administration (day 1) and intravenous infusion (day 4) is depicted in Figure 1, and the pharmacokinetic parameters derived are listed in Table 2. Following oral administration, mean peak concentrations of 2.4 mg/L were observed after 2.1 h. The mean terminal half-life was 9.9 h and the mean \( \text{AUC}_{0-\infty} \) was 34.4 mg.h/L. On day 4, the mean peak concentrations (corrected for the carry over) at the end of infusion were 4.2 mg/L and decreased with a terminal half-life of 12.2 h. The \( \text{AUC}_{0-\infty} \) was 43.7 mg.h/L. The oral bioavailability was 79.6%. The concentrations of moxifloxacin in the plasma specimens obtained after 72–120 h were 0.070±0.050 mg/L, and were systematically higher than those calculated from the

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<th>No.</th>
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<th>BMI (kg/m²)</th>
<th>IBW (kg)</th>
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<td>53.9</td>
<td>55.0</td>
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n 12 12 12 12 12 12 12
Mean 41 167 137 48.9 59.0 63.4 68.9
SD 12 8 20 4.3 8.9 11.4 12.9
Median 41 167 143 48.4 58.4 62.2 67.6
Minimum 25 151 98 43.0 44.2 47.2 49.4
Maximum 61 183 166 58.2 77.1 88.6 94.8

M, male; F, female.
Specimens of subcutaneous adipose tissue, greater omentum and small intestine were obtained during surgery 1.8–3.7 h after moxifloxacin infusion. Whereas mean (+SD) tissue concentrations in the small intestine (6.99 ± 2.34 mg/kg) were twice the concomitant plasma concentrations (3.03 ± 0.70 mg/L), the concentrations in the greater omentum (0.801 ± 0.168 mg/kg) or subcutaneous fat (0.638 ± 0.180 mg/kg) were only one-quarter of those.

**Discussion**

Moxifloxacin is approved in a fixed-dose regimen of 400 mg administered once daily. No dosage adjustment is required in the elderly, or in patients with mild hepatic or any degree of renal impairment. However, information regarding the impact of morbid obesity on the pharmacokinetics of moxifloxacin is lacking.

In the present study, we investigated the pharmacokinetics of moxifloxacin in 12 morbidly obese patients with a BMI of 43–58 kg/m² after oral administration of 400 mg of moxifloxacin and after intravenous infusion on day 4 of treatment, when steady-state conditions could be assumed. Oral administration preceded intravenous administration to determine the absolute bioavailability of moxifloxacin in this special population unaffected by the gastric bypass. The overall pharmacokinetic parameters as well as the safety and tolerability profile fitted well with historical data from healthy volunteers and patients. In agreement with common consensus, the oral bioavailability of moxifloxacin was not altered in our obese patients compared with normal-weight subjects. The shorter terminal half-life after oral administration compared with intravenous administration (10 h versus 12 h) can be explained mainly by the

**Figure 1.** Mean (+SD) plasma concentration–time course in 12 morbidly obese patients (2 male/10 female) following oral administration on day 1 (open circles) and intravenous infusion on day 4 (filled circles) of treatment with 400 mg of moxifloxacin once daily.

**Table 2.** Pharmacokinetic parameters of 400 mg of moxifloxacin in morbidly obese patients following oral administration (day 1) and intravenous infusion over 1 h (day 4)

<table>
<thead>
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<td>Tmax (h)</td>
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<tr>
<td>SD</td>
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<td>1.1</td>
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</table>

Plasma concentrations on day 4 were corrected for the residual concentrations of precedent doses, as described in the Patients and methods section.

\[ t_{1/2}^{\text{day 4}} = 0.59 \pm 0.25 \text{ mg/L}. \]
shorter sampling period due to the once daily dosage regimen (the concentrations of moxifloxacin after intravenous infusion decreased also with a half-life of 10.7 ± 2.5 h between 4 and 24 h). The even slower elimination from 48 h onwards on day 4 may be attributable to redistribution from a deep compartment. However, the sampling strategy was not designed to capture this very late phase. Since ≏ 90% of drug exposure (as measured by AUC) occurs within the first 48 h, we consider this potential additional compartment not to be of clinical relevance, at least for standard treatment regimens. It can be speculated that after long-term treatment (e.g. for tuberculosis), the progressive saturation of deeper compartments could lead to the clinically apparent accumulation of moxifloxacin.

The concentrations of moxifloxacin in the tissues of the respiratory tract,10–12 prostate,1 pancreas13 or small intestine (Wirtz et al.14 and the present study) are typically 2- or 3-fold higher than in plasma, even shortly after administration. Data on the penetration of moxifloxacin into adipose tissue are lacking. The concentrations of moxifloxacin found in the present study in the greater omentum and subcutaneous fat were very low. However, tissue homogenate cannot provide separate information on the distribution between different tissue components, such as extra- and intracellular fluid and connective structures. Thus, one cannot conclude from our data that moxifloxacin is not suitable for infections involving adipose tissue. Since tissue was sampled only in a narrow interval, we cannot describe the full concentration–time course. One could speculate that moxifloxacin penetration into adipose tissue occurs very slowly and much higher peak concentrations would be observed later in the dosing interval. In this case, however, tissue concentrations would reflect accumulation from the precedent doses. Since sampling was performed on day 4 of treatment with moxifloxacin in this study, we can exclude this scenario. In agreement with our data, similarly low concentrations in the adipose tissue of

Figure 2. Correlation of V with (a) TBW, (b) height, (c) LBW2005,6 (d) FFM and (e) IBW in 12 morbidly obese patients following intravenous infusion of 400 mg of moxifloxacin.

Moxifloxacin in obesity
morbidly obese patients were reported for trovafloxacin, while the plasma pharmacokinetics was also similar to that of healthy volunteers.\textsuperscript{15}

CL is the essential pharmacokinetic parameter to consider when devising a maintenance dose regimen. Moxifloxacin is cleared from the blood, unchanged, into the faeces and urine as well as after conjugation in the liver.\textsuperscript{9} Studies with oxazepam, lorazepam and acetaminophen have suggested that TBW-proportional increases in glucuronidation and sulphate conjugation occur in obese individuals.\textsuperscript{1} The mean total CL in our patients following intravenous infusion was 9.6 L/h, almost 20\% lower compared with healthy volunteers,\textsuperscript{9} but well within the range reported in patients.\textsuperscript{8} Apparently, the CL of moxifloxacin is not changed, and in particular not increased, in morbidly obese individuals.

Estimation of V is necessary to calculate the appropriate loading doses of antibiotics. For most antimicrobial agents, the interaction between drug pharmacokinetics and body-size indices is complex, and the most accurate size descriptor that should be taken into consideration for dosage calculation has not been firmly established.\textsuperscript{16} It has been shown that V of hydrophilic drugs, such as \( \beta \)-lactams, aminoglycosides or vancomycin, was increased in morbidly obese patients compared with normal-weight individuals\textsuperscript{3} and that drug dosing based on mass, e.g. TBW, may be an appropriate method of dose individualization.\textsuperscript{5}

In our patients, the absolute V of moxifloxacin was the same as in normal-weight volunteers,\textsuperscript{9} nearly halved when normalized to body weight and only moderately correlated with TBW. In line, V was better associated with IBW, FFM or LBW\textsuperscript{2005.6} Interestingly, to body weight and only moderately correlated with TBW. In line, a lower AUC than in normal-weight patients, the difference was a fixed garenoxacin dose of 400 mg in obese subjects resulted in the range reported in patients.\textsuperscript{8} Apparently, the CL of moxifloxacin is not changed, and in particular not increased, in morbidly obese individuals.

In conclusion, the pharmacokinetics of moxifloxacin is not significantly affected by morbid obesity. No dose adjustment seems to be necessary in this particular population.

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Transparency declarations

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References


