Population pharmacokinetics and pharmacodynamic evaluation of intravenous and enteral moxifloxacin in surgical intensive care unit patients

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Objectives: To describe the plasma concentration–time profile of moxifloxacin after intravenous and enteral administration in intensive care unit (ICU) patients and to provide a pharmacodynamic (PD) evaluation with regard to pneumonia.

Patients and methods: Twenty-five adult patients from a cardiothoracic/mixed surgical ICU were enrolled. Moxifloxacin was given as a standard dose (400 mg once daily). Therapy was successfully switched to enteral administration on day 5 in 16 patients. A rich data sampling schedule was performed after intravenous (day 4) and enteral (day 8) administration. Moxifloxacin concentrations were analysed by HPLC. A population pharmacokinetic (PK) model was developed using NONMEM VII. Simulated concentration–time profiles were evaluated for their probability of attaining PK/PD target values relevant for community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP).

Results: A linear-elimination two-compartment model described the data adequately. Parameter estimates (coefficient of variation of inter-individual variability) were: absorption rate constant, 1.09/h (135%); enteral bioavailability, 76% (20.0%); central volume of distribution, 55.6 L; peripheral volume of distribution, 59.6 L (15.3%); inter-compartmental clearance, 47.7 L/h; and clearance, 11.3 L/h (23.7%). Both intravenously and enterally administered standard-dose moxifloxacin reliably attained the PK/PD target values for pathogens with MICs ≤0.25 mg/L for CAP and ≤0.125 mg/L for HAP.

Conclusions: Drug exposure to moxifloxacin in ICU patients was more variable than in healthy volunteers. The standard dosing provides sufficient drug exposure for treatment of CAP but for HAP it does so only when a highly susceptible pathogen is present. Intravenous/enteral sequential therapy may be considered for cautiously selected cases in ICU patients.

Keywords: antimicrobial therapy, fluoroquinolones, pneumonia, bioavailability, probability of target attainment, ICUs

Introduction

Moxifloxacin exhibits good antibacterial activity against relevant Gram-negative and Gram-positive pathogens, including anaerobes and intracellular pathogens, and is hence a suitable agent for empirical treatment of a variety of infections.1,2 Among others, moxifloxacin is approved for infections of the respiratory tract, i.e. acute bacterial sinusitis, acute exacerbation of chronic bronchitis and community-acquired pneumonia (CAP).3 Due to its spectrum of activity, it is also recommended by guidelines for the treatment of hospital-acquired pneumonia (HAP) in the absence of risk factors for multidrug-resistant pathogens or Pseudomonas aeruginosa.4

As for most fluoroquinolones, oral bioavailability of moxifloxacin is good, allowing a switch from intravenous to oral administration as soon as clinical conditions have improved.
and safety of such a sequential therapy have been demonstrated for CAP. The putative benefits include reduction of costs for drug acquisition and its administration (nursing time), of catheter-related complications (e.g. thrombophlebitis and bloodstream infections) and even of length of hospitalization.

In intensive care unit (ICU) patients, important changes in volume of distribution and/or clearance can occur, significantly affecting drug exposure and possibly leading to therapeutic failure or adverse drug reactions. Plasma concentrations of moxifloxacin in septic patients have been shown to be lower and more variable than in healthy volunteers, questioning the appropriateness of standard dosing for this population. Similarly, enteral bioavailability could easily be altered due to impaired gastrointestinal motility and function, and the extent and reliability of enteral bioavailability should be confirmed before the wide use of enteral therapy in the ICU setting.

There are only limited data on the plasma pharmacokinetics (PK) of moxifloxacin in ICU patients, and there is only one preliminary report on its enteral bioavailability in four critically ill patients. Therefore, the aim of the present study was to describe the concentration–time profile of moxifloxacin after intravenous and after enteral administration in ICU patients using the population PK approach, and to provide a pharmacodynamic (PD) evaluation of the approved dosing regimen in this special population.

Patients and methods

Study design and protocol

This was an open-label, non-randomized, single-centre PK study in ICU patients. The study (EudraCT No. 2007–004941–13) was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee at the University of Tübingen. Written informed consent was obtained from all patients or their legal representative prior to inclusion in the study.

Adult patients from a surgical ICU (Department of Anesthesiology and Intensive Care, University Hospital of Tübingen, Germany) were eligible for the study if they received moxifloxacin for the treatment of an infection of the respiratory tract or of soft tissues. Main exclusion criteria were abnormal liver function tests or cirrhosis, estimated creatinine clearance <30 mL/min, known intestinal conditions that could interfere with the absorption of moxifloxacin such as inflammatory bowel disease, intra-abdominal surgery, signs of abnormal intestinal motility defined as gastric reflux >300 mL/day, vomiting or diarrhoea, or enteral co-administration of drugs containing polyvalent cations.

The prescription of moxifloxacin was at the discretion of the attending physician only and independent of potential study participation, as was co-administration of drugs containing polyvalent cations.

Population PK analysis, simulations and PD evaluation

Population PK analysis of moxifloxacin plasma concentrations was performed using non-linear mixed-effect modelling (NONMEM, version VII, ICON Development Solutions, Ellicott City, MD, USA). Data were analysed using the first-order conditional estimation method (FOCE). One-, two- and three-compartment linear-elimination models incorporating an additional absorption compartment were investigated. Model parameterization used the PREDDPP subroutine ADVAN 6 in NONMEM. The number of required digits (TOL) was set to 7.

A log-normal distribution of individual PK model parameters was assumed and implemented as an exponential function according to the equation:

$$P_{ij} = \theta_k \cdot e^{\eta_k}$$  \hspace{1cm} (1)

where $P_{ij}$ denotes the estimated value of the PK parameter $k$ for individual $i$, $\theta_k$ the typical value for the population PK parameter $k$ and $\eta_k$ the natural logarithmic difference between $P_{ij}$ and $\theta_k$.

The difference between individual model-predicted plasma concentrations ($Y_{\text{PRED},ij}$) and observed moxifloxacin data ($Y_{\text{m},ij}$) for each individual $i$ at time point $j$ is expressed as residual variability. This residual variability was expressed using a combined proportional ($\epsilon_{p,ij}$) and additive ($\epsilon_{a,ij}$) model:

$$Y_{\text{m},ij} = Y_{\text{PRED},ij} (1 + \epsilon_{p,ij}) + \epsilon_{a,ij}$$  \hspace{1cm} (2)

The final base model was selected on the basis of the plausibility and precision of parameter estimates, model stability, goodness-of-fit (GOF) plots and visual predictive check (VPC): a decrease in the objective function value $\geq 3.84$ ($P \leq 0.05$, $df = 1$) was considered significant for statistical comparison of the investigated nested models. A non-parametric bootstrap analysis ($n = 1000$) was performed for estimation of parameter precision (relative standard error). GOF was graphically assessed from observed versus model-predicted moxifloxacin concentration plots. VPCs were based on 1000 simulated concentration–time profiles of the investigated models and contained all measured moxifloxacin concentrations as well as the corresponding 10th, 50th and 90th percentiles of the simulated concentration–time profiles.

Body weight, age, height, sex, administration of opioids or catecholamines, creatinine clearance estimated by the Cockcroft–Gault formula and sequential organ failure assessment score (SOFA) were investigated as covariates in explaining inter-individual variability of PK parameter estimates. Covariate analysis was performed using the stepwise forward inclusion ($P \leq 0.05$, $df = 1$, $\Delta$objective function value $\Delta$OFV = $-3.84$) and backward deletion procedure ($P \leq 0.001$, $df = 1$, $\Delta$OFV = $+10.81$). Continuous covariate relations ($\xi_{\text{COV}}$) on PK parameters were implemented as a proportional change in the typical PK parameter value by one unit of a covariate value and centred around the median of the covariate (Equation 3). Dichotomous covariate influences ($\xi_{\text{COV}}$) were implemented as fractional change from one covariate category to the other as described.
Intravenous/enteral moxifloxacin in ICU patients

Results

In total, 25 patients were enrolled in the study. Reasons for admission were cardiothoracic surgery (n=15), polytrauma (n=3), severe head injury (n=2), intracranial haemorrhage (n=1), retropharyngeal tumour (n=1) and medical conditions without or after minor surgery (n=3). All enrolled patients had no risk factors for multidrug-resistant pathogens or P. aeruginosa, and received moxifloxacin for suspected pneumonia, classified as community-acquired (onset ≤48 h after hospitalization) in 14 and as hospital-acquired (onset >48 h and <5 days after hospitalization) in 11 cases. At least one plausible pathogen was cultured from respiratory secretions in 13 patients (two Staphylococcus aureus, two Haemophilus influenzae, one Haemophilus parainfluenzae, two Klebsiella pneumoniae, two Enterobacter cloacae, three Serratia marcescens, one Hafnia alvei, one Proteus mirabilis and one non-fermenting Gram-negative bacillus). Susceptibility to moxifloxacin was not routinely tested. No patient with skin or soft tissue infection was included. Further patient characteristics are shown in Table 1. All 25 patients completed period 1. In one patient, switch to enteral therapy was not possible due to high gastric reflux. Moxifloxacin was discontinued before period 2 in two patients due to suspected adverse reactions (elevation of creatinine levels in both and additional QT prolongation in one patient), in one patient because of complete resolution of signs and symptoms and in one patient because a non-susceptible pathogen was detected. One patient died of his underlying cardiac disease and three were discharged from the ICU and unavailable for period 2. Thus, 16 patients underwent both (intravenous and enteral) study periods.

PK analysis and PD evaluation

The individual plasma concentration–time profiles of moxifloxacin following intravenous (day 4) and enteral (day 8) administration are depicted in Figure 1. Median peak and trough concentrations were 4.9 and 0.46 mg/L after intravenous administration, and 2.7 and 0.27 mg/L after enteral administration, respectively. The observed moxifloxacin concentrations were best described (GOF, Figure 2) and predicted (VPC, Figure 3) by a linear-elimination two-compartment model with a combined additive and proportional residual variability model. Parameter estimates of the final model are summarized in Table 2. The bootstrap analysis demonstrated acceptable precision for all parameters (Table 2). Estimated creatinine clearance was the only significant covariate, explaining ~20% of inter-individual variance in clearance. Moxifloxacin clearance declined by 0.44 L/h per 10 mL/min reduction in creatinine clearance. However, this result was mainly driven by three patients with low creatinine clearance and extraordinarily high AUC 24h, whereas in the majority of patients no trend was visible (Figure 4). Therefore, as the final model the one without covariate influence was used for simulations.

The distribution of the simulated AUC 24h was in good agreement with the individually observed values (data not shown). The PTAs according to indication and MIC of a causative pathogen are shown in Figure 5. In brief, all simulated modalities provided reliable (PTA >90%) target attainment for pathogens with MICs up to 0.25 and 0.125 mg/L in CAP and HAP, respectively, but were unable (PTA <5%) to attain the targets for pathogens with

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients in period 1 (n=25)</th>
<th>Patients in period 2 (n=16)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>64 (18–78)</td>
<td>60.5 (18–78)</td>
</tr>
<tr>
<td>Sex (no. of males/no. of females)</td>
<td>20/5</td>
<td>14/2</td>
</tr>
<tr>
<td>Total body weight (kg)</td>
<td>81 (55–109)</td>
<td>80 (55–109)</td>
</tr>
<tr>
<td>APACHE II score at admission</td>
<td>15.5 (9–21)</td>
<td>15.5 (11–21)</td>
</tr>
<tr>
<td>Estimated creatinine clearance (mL/min)</td>
<td>89 (22–226)</td>
<td>78 (22–226)</td>
</tr>
<tr>
<td>SOFA</td>
<td>8 (3–14)</td>
<td>9 (6–14)</td>
</tr>
<tr>
<td>Administration of catecholamines</td>
<td>6 (2–13)</td>
<td>6 (4–13)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>8 (2–11)</td>
<td>7 (2–11)</td>
</tr>
</tbody>
</table>

aMedian (minimum–maximum).

bNumber (percentage of total).
MICs of 1.0 and 0.5 mg/L, respectively, or higher. For the MICs in between (0.5 mg/L for CAP and 0.25 mg/L for HAP), PTA ranged from 27% to 71%, defining an intermediate category.

Discussion

Moxifloxacin is approved in a flat dosing regimen of 400 mg once daily for both intravenous and oral administration. No dosage adjustment is required in the elderly or in patients with mild hepatic or any degree of renal impairment. Although precisely these features are very frequent in ICU patients, their acute physiological disturbance—compared with stable chronic disease—calls for specific data on the PK properties of moxifloxacin in this special population. Limited PK data are available for mechanically ventilated patients with pneumonia, for patients with peritonitis and for patients with severe sepsis or septic shock, i.e. in specific critical conditions. Generally, these studies reported increased clearances compared with healthy volunteers, possibly leaving a relevant proportion of patients with low drug exposure as measured by AUC. Data for a more mixed ICU population are lacking.

In the present study, we firstly provide a population PK model for intravenously and enterally administered moxifloxacin in moderately ill, surgical ICU patients. Compared with healthy volunteers, average volume of distribution and clearance were similar, but clearance was more variable. Estimated creatinine clearance could explain ~20% of inter-individual variability in drug clearance, which is in good agreement with the renally excreted drug fraction. In contrast to our results, clearance of moxifloxacin was found not to be affected by stable chronic renal disease. It is argued that alternative routes of elimination (i.e. excretion into the faeces of the unchanged or conjugated drug) fully compensate the reduced renal excretion of moxifloxacin in these patients. In ICU patients, reduced creatinine clearance may be representative of global organ dysfunction rather than isolated renal dysfunction, explaining the more pronounced...
impact on drug clearance. Nonetheless, since unexplained variability prevails and moxifloxacin is generally well tolerated, we would not recommend dose reduction in patients with acute renal impairment. Moreover, despite its statistical significance, the result is driven by very few observations (see Figure 4). Unfortunately, patients with an estimated creatinine clearance <30 mL/min were not enrolled (except for one who was included by mistake), and only four patients had an estimated creatinine clearance < 60 mL/min. Therefore, our study provides an insufficient basis for conclusions in this range. The impact of acute renal impairment on drug clearance.

**Table 2.** Parameter estimates of a population PK model of moxifloxacin in ICU patients

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Unit</th>
<th>Estimate</th>
<th>Relative standard error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>L/h</td>
<td>11.3</td>
<td>31</td>
</tr>
<tr>
<td>Central volume of distribution</td>
<td>L</td>
<td>55.6</td>
<td>48</td>
</tr>
<tr>
<td>Peripheral volume of distribution</td>
<td>L</td>
<td>59.6</td>
<td>19</td>
</tr>
<tr>
<td>Inter-compartmental clearance</td>
<td>L/h</td>
<td>47.7</td>
<td>18</td>
</tr>
<tr>
<td>Absorption rate constant</td>
<td>1/h</td>
<td>1.09</td>
<td>42</td>
</tr>
<tr>
<td>Enteral bioavailability</td>
<td>%</td>
<td>76.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Inter-individual variability (coefficient of variation) in clearance</td>
<td>%</td>
<td>23.7</td>
<td>39</td>
</tr>
<tr>
<td>in peripheral volume of distribution</td>
<td>%</td>
<td>15.3</td>
<td>42</td>
</tr>
<tr>
<td>in absorption rate constant</td>
<td>%</td>
<td>135</td>
<td>41</td>
</tr>
<tr>
<td>in enteral bioavailability</td>
<td>%</td>
<td>20.0</td>
<td>41</td>
</tr>
<tr>
<td>Residual variability (coefficient of variation) proportional error</td>
<td>%</td>
<td>12.6</td>
<td>42</td>
</tr>
<tr>
<td>additive error</td>
<td>mg/L</td>
<td>0.02</td>
<td>43</td>
</tr>
</tbody>
</table>

**Figure 3.** VPC of the final model after multiple dosing of moxifloxacin in ICU patients.

**Figure 4.** AUC24 of 400 mg of moxifloxacin after multiple intravenous and enteral administration versus creatinine clearance in ICU patients. Measurements performed in the same patient on different days are connected.

**Figure 5.** PTA versus MIC functions for 400 mg of moxifloxacin once daily in ICU patients for CAP (F AUC24/MIC > 34) and HAP (F AUC24/MIC > 75) after the first intravenous dose, after multiple intravenous dosings and after multiple enteral dosings. Data points above the horizontal line (PTA > 0.9) indicate acceptable reliability of the dosing regimen.
renal dysfunction in critically ill patients on the PK of moxifloxacin may merit exploration in a specific study.

Enteral bioavailability in this study was lower and more variable than in healthy volunteers.18 This could be specific to the studied population or caused by crushing the tablet and administering it through a nasogastric tube, which has been shown in healthy volunteers to decrease the bioavailability by 9% compared with ingestion of the intact tablet.20 To summarize, based on average PK parameters, no dose adjustments for intravenous dosing seem warranted in ICU patients, whereas enteral administration is not reliable.

Apart from simply considering only average PK parameters, we also evaluated the appropriateness of the dosing regimen with regard to its capacity to attain PK/PD targets associated with efficacy. A reliable dosing regimen would attain the target in a high fraction (e.g., >90%) of treated patients or, synonymously, would have a high PTA. PTA is a function of the (lower) extremes of a population rather than its average values—PTA is >90% if a patient on the 10th percentile reaches the target, no matter by how much the average of the population will exceed it. Therefore, the PTA approach allows determination of dosage regimens ensuring effective antibiotic drug concentrations for the large majority of treated patients. Dosing recommendations based on PTA can differ from conclusions derived from average PK parameters. For fluoroquinolones, AUC0–24/MIC is considered to be the clinically relevant PK/PD index,17 and various target values have been established, e.g. for clinical cure, pathogen eradication or suppression of resistance.21,22 The PD evaluation of an intravenous/enteral sequential therapy with moxifloxacin investigated in the present study yields two main results. First, the three simulated modalities—first intravenous dose, steady state after intravenous administration and steady state after enteral administration—showed similar PTA versus MIC functions within both indications. Regarding target attainment, all three modalities would be identically categorized as reliable, intermediate or unacceptable, respectively, for a given MIC. Therefore, one would neither suggest initiation with a higher loading dose nor discourage switching to enteral dosing. However, it should be emphasized that the concentration–time profile after the first intravenous dose was simulated on the basis of parameters obtained during steady state and was not actually determined. The underlying assumption of constant PK properties over time seems justified for the present purpose, although ICU patients especially are most likely to undergo significant pathophysiological changes within a few days or even hours. Given the high importance of early and appropriate initiation of antimicrobial therapy,23,24 precise PK information and better understanding of PK/PD interactions within the first dosing interval is most desirable.

The second result is that the PK/PD targets were reliably attained only for pathogens with a MIC of ≤0.25 or ≤0.125 mg/L for CAP and HAP, respectively. Whereas isolates in CAP such as Streptococcus pneumoniae and H. influenzae usually have MICS <0.25 mg/L, typical HAP pathogens like Enterobacteriaceae frequently present MICS >0.125 mg/L.25 These results support the use of standard-dose moxifloxacin and in particular intravenous/enteral sequential therapy as a reasonable choice for the treatment of CAP, but question its value as a therapeutic option in the case of HAP unless a highly susceptible pathogen is proven.

We chose readily available and accepted target values for successful therapy of community-acquired respiratory tract infections (AUC0–24/MIC >34) and of nosocomial pneumonia (AUC0–24/MIC >75).17 These targets are rather low. One could argue that the fastest possible eradication and reliable suppression of resistance should be sought in ICU patients, given their individual vulnerability and the high risk of spread of resistant pathogens to other patients as well. This would call for higher target values (up to >250),26 shifting the PTA versus MIC function to the left, i.e. to even lower MICs. Accordingly, standard-dose moxifloxacin monotherapy would be appropriate only for the most susceptible pathogens.

Although this concept of PK/PD evaluation is well established and should be integrated into clinical trial design,27 some shortcomings are evident. First, clinical PK/PD target values are usually derived from retrospective analysis of clinical trials that have been pooled across different indications and different substances of the same antimicrobial class. Differences in protein binding between substances are usually accounted for by fixed factors, as we did in our analysis, neglecting part of the actual individual variability. Second, such an evaluation is only a statistically linked surrogate for clinical outcome, and could easily be refuted by divergent results from clinical trials. To our knowledge, however, there is only one clinical trial of moxifloxacin in HAP, which was prematurely terminated due to slow recruitment.28 This trial enrolled patients with mild to moderate nosocomial pneumonia and excluded patients with an APACHE II score >20. Moxifloxacin showed non-inferiority compared with intravenous ceftriaxone followed by oral cefuroxime axetil. Another clinical trial compared moxifloxacin and ampicillin/sulbactam in patients with aspiration pneumonia, which is bacteriologically similar to HAP with a predominance of S. aureus and Enterobacteriaceae.29 The cure rate was similarly low in both treatment groups (67%). We would therefore argue that standard-dose moxifloxacin has not convincingly been proved to be effective in the treatment of HAP. If such studies should be attempted, special consideration should be given to exploring the PK/PD relationship. In the meantime, clinicians who consider moxifloxacin for the treatment of HAP in compliance with current guidelines should be aware of its limited ability to attain PK/PD targets for pathogens with moderate or low susceptibility.

Conclusions

We present a population PK model for surgical ICU patients with a moderate degree of illness for both intravenous and enteral administration of standard-dose moxifloxacin. PD evaluation indicates a good probability of clinical success for CAP, but calls for caution in the treatment of HAP unless a highly susceptible pathogen is proven. Although enteral bioavailability of moxifloxacin is reduced and less reliable than in other populations, intravenous/enteral sequential therapy may be considered for cautiously selected cases even in ICU patients.

Acknowledgements

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Intravenous/enteral moxifloxacin in ICU patients

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Transparency declarations

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