Single- and multiple-dose pharmacokinetics of intravenous moxifloxacin in patients with severe hepatic impairment

Jürgen Barth1*, Doris Jäger1, Ralf Mundkowski2, Bernd Drewelow2, Tobias Welte3 and Olaf Burkhardt3

1Department of Internal Medicine, BG Clinic Bergmannstrost, Halle/Saale, Germany; 2Institute of Clinical Pharmacology, University Rostock, Rostock, Germany; 3Department of Pulmonary Medicine, Medical School Hannover, Hannover, Germany

Received 19 November 2007; returned 19 February 2008; revised 18 March 2008; accepted 28 April 2008

Objectives: The aim of this study was to investigate the single- and multiple-dose pharmacokinetics (PK) of moxifloxacin and its penetration into ascitic fluid in patients with severe liver insufficiency (Child–Pugh class C).

Patients and methods: In a single-centre, prospective, open-label study, nine adult cirrhosis patients were treated with 400 mg moxifloxacin infusion once a day. On days 1 and 3, drug concentrations in serum and ascites were determined before and at different time points up to 24 h after medication with a validated HPLC method.

Results: On day 1, serum concentrations of moxifloxacin decreased from a median of 3.7 mg/L at 1 h to 0.6 mg/L at 24 h. On day 3, serum peak and trough levels were only moderately increased in comparison with day 1, with moxifloxacin concentrations of 3.9 mg/L after 1 h and 0.6 mg/L 24 h after the third infusion. The AUC values were also slightly, but not statistically significantly, increased on day 3. Calculations of $t_{1/2}$, mean residence time, $CL_{tot}$ and $V_{ss}$ revealed no significant differences between days 1 and 3. Median concentrations of moxifloxacin in ascitic fluid were 1.4 mg/L (3 h after infusion) and 1.3 mg/L (6 h) on day 1 and 2.1 mg/L (3 h) and 1.9 mg/L (6 h) on day 3. Median ascites/serum ratios did not vary between days 1 and 3.

Conclusions: PK parameters of moxifloxacin in patients with advanced liver cirrhosis differed only marginally from those from healthy control groups given in the literature. After multiple dosing, no drug accumulation was seen. Therefore, we conclude that a dose adjustment is not necessary in this patient group. Ascitic fluid reached bactericidal levels for common bacteria found in spontaneous bacterial peritonitis.

Keywords: fluoroquinolones, chronic liver insufficiency, Child C, ascites

Introduction

Severe bacterial infections such as spontaneous bacterial peritonitis, pneumonia or sepsis are well-described life-limiting complications in patients with advanced liver cirrhosis. Pharmacological and microbiological characteristics make moxifloxacin an attractive option in the treatment of severe bacterial infections independently of the infection site. On the other hand, since moxifloxacin is predominantly metabolized by the liver, a theoretical drug accumulation cannot be excluded in patients with advanced liver insufficiency. Owing to the lack of appropriate pharmacokinetic data, the use of moxifloxacin is currently not recommended in this patient population. The purpose of this study was to document the pharmacokinetic profile of intravenous moxifloxacin in patients with severe hepatic impairment (Child–Pugh class C) after single and multiple dosing. In addition, we investigated the ability of the drug to penetrate into ascitic fluid at the site of infection in spontaneous bacterial peritonitis.

Patients and methods

Study design and subjects

This single-centre, prospective, open-label study was performed on a cohort of nine adult patients with alcoholic liver cirrhosis and
advanced liver failure (Child–Pugh score >9 points) admitted to the Department of Internal Medicine, BG Clinic Bergenstromst, Halle/Saale, Germany. All patients were regularly treated with 400 mg of intravenous moxifloxacin (Avelox® I.V., Bayer HealthCare AG, Wuppertal, Germany) over 1 h once daily for pneumonia (n = 3) or spontaneous bacterial peritonitis (n = 6), irrespective of their body weight, age and sex. Exclusion criteria were: child-bearing potential, pregnancy, lactation, a severely immunocompromised status, use of any antibacterial agent 4 weeks before study entry, severe renal impairment (creatinine clearance <30 mL/min/1.73 m² or haemodialysis), significant cardiovascular disease, severe psychiatric disease, a history of drug abuse and known allergy to fluoroquinolones. All patients were given a detailed description of the study, and their written consent was obtained. The protocol of the study was approved by the local institutional review board. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guideline of the European Commission. Tolerability and safety assessments, clinical chemistry, haematological tests and urinalysis, and the measurement of vital signs (blood pressure and heart rate) and ECG were included in the study. All data relating to drug safety were recorded throughout the study.

**Moxifloxacin sampling and analysis**

On day 1, blood samples (6 mL) were taken from a peripheral vein before and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 h after start of infusion through an indwelling venous cannula, and on day 3 (steady-state) before and 1, 2, 3, 6 and 24 h after medication. The samples were centrifuged at 2800 g for 5 min at 4 °C and stored at –80 °C until analysis. Additionally, in five patients, where paracentesis was clinically indicated, samples of ascitic fluid (~50 mL per sample) were obtained 3 and 6 h after infusion on days 1 and 3. Concentrations of moxifloxacin in serum and ascites samples were determined by the HPLC method with fluorescence detection. The assay was validated intra- and inter-daily according to standard procedures. The lower limit of quantification of moxifloxacin was ≤0.01 mg/L in serum and ascitic fluid, with coefficient of variation and relative error of <5% and <1%, respectively. Precisions 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.

**Pharmacokinetic analysis**

Non-compartmental pharmacokinetic analysis for the data was performed using the WinNonlin software program (WinNonlin version 3.1, Pharsight Corporation, Mountain View, CA, USA). The maximum concentration in plasma (C\text{max}) and time to reach C\text{max} (T\text{max}) after drug administration were obtained directly by visual examination of concentration–time data. The area under the plasma concentration–time curve from time zero to infinity (AUC\text{0–}\infty) was calculated by log-linear trapezoidal rule until the time of last quantifiable plasma concentration and then extrapolated to infinity by using the quotient of the last measurable concentration (C\text{last}) to the terminal-phase rate constant (β). The terminal elimination rate constant (β) was estimated from the slope of terminal exponential phase of the logarithmic plasma concentration–time profile, using at least three data points. The elimination half-life (t1/2\beta) was determined as 0.693/β. The mean residence time (MRT) was calculated AUMC\text{0–}\infty/AUC\text{0–}\infty, where AUMC\text{0–}\infty is the area under the first moment of the concentration–time curve. Total body clearance (CL\text{tot}) was determined as dose/AUC\text{0–}\infty. The steady-state volume of distribution (V\text{ss}) was calculated as a product of MRT and CL\text{tot}.

All data are presented as median and minimum–maximum ranges. Statistical analysis for differences in pharmacokinetic parameters from day 1 to day 3 was performed using the Wilcoxon signed-rank test. P values <0.05 were considered significant.

**Results**

Nine patients (1 woman, 40 years old, and 8 men, aged between 40 and 78 years; median body weight 82 kg, range 68–92 kg) with alcoholic liver cirrhosis and severe hepatic impairment (Child–Pugh class C) were included in the study. The creatinine clearance of the patients varied between 65 and 121 mL/min/1.73 m². No hypoalbuminaemia was observed. All included patients had clinical signs of infection, including leucocytosis and an elevated C-reactive protein. The most common diagnosis was spontaneous bacterial peritonitis (six patients), verified by detection of >250 neutrophils/µL in ascitic fluid. Median length of moxifloxacin treatment was 7 days. Overall tolerability of the treatment with moxifloxacin was good. No serious adverse events were observed. No patient had to be withdrawn from the study. Pharmacokinetic investigations in serum were completed for all nine patients. The serum concentration–time curves of days 1 and 3 are shown in Figure 1. All relevant pharmacokinetic parameters after single (day 1) and multiple (day 3) administration are listed in Table 1. On day 1, serum concentrations of moxifloxacin were highest at the end of the 1 h infusion, with a median of 3.7 mg/L, and decreased progressively during the sampling period, reaching a median of 0.6 mg/L at 24 h. On day 3, serum peak and trough levels were only moderately increased in comparison with day 1, with moxifloxacin concentrations of 3.9 mg/L after 1 h and 0.6 mg/L 24 h after the third infusion (Figure 1). The AUC\text{0–24} (31.8 versus 37.4 mg·h/L) and AUC\text{0–}\infty (41.9 versus 45.5 mg·h/L) were slightly, but not statistically significantly, increased on day 3. Calculations of terminal elimination half-life, MRT, CL\text{tot}, and V\text{ss} in serum also revealed no significant differences between days 1 and 3 (Table 1). In the ascitic fluid median (range), concentrations of moxifloxacin were 1.4 mg/L (1.0–2.1 mg/L) 3 h after infusion and 1.3 mg/L (1.2–1.8 mg/L) 6 h after the infusion of moxifloxacin (Figure 1).
Table 1. Pharmacokinetic parameters [median (range)] of moxifloxacin in serum of patients (n = 9) with severe chronic liver insufficiency (Child C) on days 1 and 3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Single dose (day 1)</th>
<th>Multiple dose (day 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (mg/L)</td>
<td>3.7 (2.8–4.2)</td>
<td>3.9 (2.9–4.1)</td>
</tr>
<tr>
<td>C\text{AUC}_{0–24} (mg h/L)</td>
<td>31.8 (22.4–38.7)</td>
<td>37.4 (28.8–44.8)</td>
</tr>
<tr>
<td>T\text{max} (h)</td>
<td>1 (1–1)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td>AUC\text{C}_{1/2} (mg h/L)</td>
<td>41.9 (32.1–56.7)</td>
<td>45.5 (38.1–62.2)</td>
</tr>
<tr>
<td>t\text{1/2} (h)</td>
<td>12.0 (8.4–13.3)</td>
<td>10.4 (8.5–16.0)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>17.0 (10.9–18.9)</td>
<td>14.4 (10.4–23.5)</td>
</tr>
<tr>
<td>Cl\text{tot} (L)</td>
<td>10.0 (7.1–14.2)</td>
<td>8.8 (6.4–10.5)</td>
</tr>
<tr>
<td>V\text{ss} (L)</td>
<td>154.1 (118.5–216.1)</td>
<td>104.3 (92.4–161.6)</td>
</tr>
</tbody>
</table>

No significant differences in pharmacokinetic parameters from day 1 to day 3 (Wilcoxon’s signed-rank test, P > 0.05).

infusion on day 1, and 2.1 mg/L (1.7–2.4 mg/L) 3 h after infusion and 1.9 mg/L (1.5–2.2 mg/L) 6 h after infusion on day 3. There were no significant differences in median moxifloxacin penetration into ascites, calculated as ascites/serum concentration ratio (day 1: 0.6 at 3 h versus 0.9 at 6 h; day 3: 0.7 at 3 h versus 0.8 at 6 h).

Discussion

Although intravenous moxifloxacin is widely used in the treatment of serious hospital infections, no study investigating its single- and multiple-dose pharmacokinetics (PK) in patients with hepatic insufficiency has been published previously. As our results have shown, moxifloxacin can be safely administered to subjects with liver cirrhosis and severe hepatic impairment (Child–Pugh class C) without the need for dose adjustment. The main pharmacokinetic parameters of moxifloxacin such as peak and trough serum concentrations, AUC values, terminal elimination half-life, MRT, total body clearance and volume of distribution in our study were absolutely comparable with previous reports in healthy young and older volunteers.4,6 Beyond that, neither statistically significant nor clinically relevant differences were observed between the pharmacokinetic profiles of moxifloxacin on days 1 and 3. A possible explanation for the lack of drug accumulation in our patients might be related to the unique liver metabolism of moxifloxacin alone via glucuronide and sulphate conjugation. According to Stass and Kubitzka,5 ~54% of a single dose is recovered in stool and urine as metabolite M1 (sulfo metabolite) and M2 (acyl metabolite), ~45% of an intravenous dose of moxifloxacin is excreted as unchanged drug, 20% in urine and 25% in faeces. In general, it is well known that chronic liver diseases are associated with impaired metabolism of a number of drugs.7 However, the degree of impairment varies depending on the type of metabolic reaction involved. Oxidative metabolic reactions, catalysed by a large number of cytochrome P450 isoenzymes, appear to be more affected by chronic liver disease compared, for example, with glucuronidation, an important Phase II reaction catalysed by the uridine diphosphate-glucuronosyltransferases.8 The cytochrome P450 system is not involved in moxifloxacin metabolism.4,6

The second aim of this study was to determine the concentrations of moxifloxacin in ascitic fluid. Here, the median concentrations following a single intravenous dose of 400 mg were 1.4 mg/L at 3 h after the end of infusion and 1.3 mg/L at 6 h after infusion. After the third infusion (day 3), median concentrations in ascites were slightly increased compared with day 1 (2.1 mg/L at 3 h and 1.9 mg/L at 6 h). The median ratios of ascites to serum concentration varied between 0.6 (day 1) and 0.8 (day 3), and were higher than that measured with ciprofloxacin, pefloxacin and ofloxacin.9 Finally, the question arises as to whether the drug concentration in the ascitic fluid is sufficient to eliminate the bacteria in patients with spontaneous bacterial peritonitis. Fluoroquinolones exert their killing effect in a concentration-dependent manner.10 Antibiotics that exhibit this pattern of killing generate a higher rate and extent of killing with increasing concentrations. Therefore, the peak of concentration (C\text{max}) and the exposure (AUC) are the most important factors associated with therapeutic efficacy. C\text{max} values 10-fold higher than the MIC\text{90} are usually considered to be effective.10 In this study, peak concentrations of moxifloxacin in ascitic fluid amounted to 175- to 260-fold of an MIC\text{90} value of 0.008 mg/L. Thus, effective ascites peak concentrations were achieved for Escherichia coli, which is the most common pathogen in spontaneous bacterial peritonitis (40% to 60% of cases).1,2 Another important PK/PD parameter for prediction of clinical efficacy in fluoroquinolones is the free AUC\text{C}_{1/2–\infty}/MIC ratio.10 Because of the limitation of only two available measuring points from the puncture of ascites, this study has not allowed the calculation of AUC in ascitic fluid from time zero to infinity.

In conclusion, this study indicated for the first time that pharmacokinetic parameters of moxifloxacin in patients with advanced liver cirrhosis after single and multiple intravenous dosing differed only marginally from those derived from healthy control groups given in the literature. After multiple dosing, no drug accumulation was observed. Therefore, a dose adjustment is not necessary in cirrhosis patients with severe hepatic impairment. Furthermore, the results of the study show that moxifloxacin penetrated ascitic fluid in cirrhosis patients, achieving and maintaining concentrations higher than the MICs for the common causative pathogens in spontaneous bacterial peritonitis.

Funding

This study was an investigator-initiated trial and was supported in part by a grant from Bayer HealthCare AG, Wuppertal, Germany.

Transparency declarations

J. B. has received research grants from Bayer HealthCare AG. B. D. has served as a consultant to and has received research grants from Bayer HealthCare AG. T. W. has served as a consultant to and has received research grants from Bayer HealthCare AG. O. B. has received research grants from Bayer HealthCare AG. The remaining authors have none to declare.
References