Clearance of moxifloxacin during continuous haemofiltration (CVVHF) in vitro

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Background/aims: The clearance of moxifloxacin is reported to be unaltered in the presence of renal insufficiency. There is little information about the clearance of intravenous moxifloxacin in renal replacement therapies during intensive care. The aim of this study was to determine the clearance of moxifloxacin during continuous veno-venous haemofiltration (CVVHF) in vitro.

Methods: The elimination of moxifloxacin (reservoir with 600 mL of washed human erythrocytes, 100 mL of NaHCO₃ and various amounts of Ringer solution and human albumin to give a total volume of 1000 mL, pH 7.35 ± 0.5; haematocrit 41 ± 2) during CVVHF in vitro with two filter conditions (during priming, after priming), three protein concentrations (human albumin: 0 g/L, 20 g/L, 40 g/L) and two filtration velocities [(i) standard condition: blood flow at 100 mL/min and turnover of 2 L/h; (ii) blood flow at 50 mL/min and turnover of 1 L/h] were investigated.

Results: A new filter needs 20 min of priming before moxifloxacin reaches a steady relative filtration rate. The sieving coefficient with 0 g/L albumin was 1.07, with 20 g/L 0.90 and with 40 g/L 0.80. Under standard filtration conditions (i) the renal clearance was between 26.7 and 35.7 mL/min, and under the altered conditions (ii) it was 15.2 mL/min.

Conclusion: During CVVHF in vitro we found filtration clearances of moxifloxacin of the same order as its renal clearance in healthy subjects. The high sieving coefficient, nearly independent of blood protein concentration, would suggest that moxifloxacin is filtered almost as freely as creatinine. These results do not indicate a need for dose adjustment under appropriate haemofiltration conditions and normal hepatic function.

Keywords: antibiotics, dosage recommendations, renal failure, renal replacement therapy, artificial membranes

Introduction

Moxifloxacin is a broad-spectrum fluoroquinolone.1 It belongs to a group of quinolones known as 8-methoxy fluoroquinolones and is effective against both Gram-positive and Gram-negative bacteria.1

Moxifloxacin, when taken orally, is well absorbed with an absolute bioavailability of ~90%. Approx. 45% is bound to serum proteins, independent of concentration.1 The renal clearance of moxifloxacin in healthy subjects is 24–53 mL/min and the total body clearance is 179–246 mL/min.2 Moxifloxacin is metabolized through glucuronide and sulphate conjugation and 19% is excreted unchanged in the urine.3 The area under the concentration–time curve (AUC) and peak concentration of moxifloxacin may be reduced in patients with mild hepatic insufficiency. The pharmacokinetics in patients with mild, moderate or severe renal impairment are not significantly altered.3

Continuous veno-venous haemofiltration (CVVHF) is an established method of continuous renal replacement therapy that offers high haemodynamic stability, optimal control of circulating volume and effective removal of metabolic products and drugs.4 For all antibiotics, pharmacokinetic data are needed for adjustment of dose and dosage interval to provide effective concentrations at the site of infection, as well as to avoid accumulation.

Recently, Fuhrmann et al.5 found that the pharmacokinetics of moxifloxacin in nine critically ill patients with acute renal failure during CVVHDF were comparable to those in patients without

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renal impairment and recommended 400 mg moxifloxacin intravenously (iv) once daily in anuric patients during CVVHDF.

The aim of this in vitro study was to determine the clearance of moxifloxacin during CVVHF in vitro under different protein concentrations and turnover conditions.

**Methods**

**Model of CVVHF**

In vitro models of renal displacement therapies are well suited to experiments on evaluation of drug removal.6,7

We used an in vitro extracorporeal circuit, originating from and terminating in a Y-shaped double-lumen catheter, which was inserted in a reservoir filled with a mixture of human blood (600 mL of washed human erythrocytes), 100 mL of 8.4% NaHCO₃ and various amounts of Ringer solution and human albumin to give a total volume of 1000 mL (pH 7.35 ± 0.5, haematocrit 41 ± 2). Blood was driven through the circuit by means of an Edwards BM 11 post-dilution haemofiltration system using SH-Bic 35 filtration solutions and Hospal Multiflow 100 haemofilters (AN69 HF, acrylonitrile sodium methallylsulphonate hollow-fibre, surface area of 0.9 m², priming volume of the filter 65 mL, line dead-volume of 75 mL). All experiments were performed at the same place in an air-conditioned room in the Department of Transfusion Medicine (22°C).

Blood samples were centrifuged (Heraeus Megafuge 1.0R, 3000g) after sampling and stored together with ultrafiltrate samples at –20°C. To ensure that the mixtures of blood could not influence the pharmacokinetics of moxifloxacin, we added 15 mg of moxifloxacin to 10 mL of the experiments’ blood mixtures (nominal concentration 1.5 mg/mL) (see below) and compared each with a mixture of 15 mg of moxifloxacin and 10 mL of fresh human blood (nominal concentration 1.5 mg/mL).

**HPLC**

A modified method for detecting moxifloxacin in plasma and dialysate was used.8 The HPLC was an Agilent 1090 with an Agilent 1046a fluorescence detector working at 296 nm excitation and 504 nm emission wavelength. A binary gradient [solvent A: 10% acetonitrile (HPLC Grade, Mallinckrodt Baker, Deventer, Holland) and 90% 40 mM (NH₄)₂HPO₄ (Fluka, Steinheim, Germany), pH 6; solvent B: 50% acetonitrile and 50% 40 mM (NH₄)₂HPO₄, pH 6] separated the target substance on a 150 × 4.6 mm diameter Luna 5µ C18(2) column (Phenomenex, Aschaffenburg, Germany) equipped with a 4 × 3 mm pre-column. The gradient started at a flow rate of 1 mL/min with 10% solvent B. It changed linearly after 1 min to 30% B at 10 min.

One hundred microlitres of plasma or dialysate was treated with 10 µL (109 ng) of internal standard ofloxacin and 1.8 mL of –20°C cold acetonitrile. Samples were centrifuged for 10 min at 13,000 rpm and the supernatant was transferred into conical glass tubes. After evaporation at 50°C in a stream of nitrogen the residual was resolved in 100 µL of solvent A, centrifuged again and transferred into 300 µL microvials. Twenty microlitres was injected into the HPLC. The limit of detection was at 12.4 ng/100 µL extracted plasma and intra- and inter-day variability were below 5% at a spike level of 1.75 µg/mL plasma.

**Experiments**

In all experiments, we had a net fluid balance of ±1 L/h; in experiments 1–4, a turnover rate of 2 L/h (post-dilution with 2 L/h, filtration rate of 2 L/h) and in experiment 5 a turnover rate of 1 L/h (post-dilution with 1 L/h, filtration rate of 1 L/h). Therefore, we had no dilution or concentration of the reservoir content. Details of the experiments are shown in Table 1.

**Calculations**

The AUCs of the moxifloxacin concentrations were calculated with the computer program Kinetica 2000 (www.innaphase.com). Calculation of filtrate clearances (CLf; CLf = Cf × Qf/Ca; Cf = filtrate concentration, Qf = filtration rate = rate of filtration fluid crossing the filter, Ca = arterial serum concentration), sieving coefficients (SC; SC = Qf/Ca),

<table>
<thead>
<tr>
<th>Experiment</th>
<th>CVVHF conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>CVVHF for 1 h, blood flow 100 mL/min, flow of isotonic replacement fluid 2 L/h (turnover 2 L/h)</td>
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<tr>
<td>5</td>
<td>CVVHF for 1 h, blood flow 50 mL/min, flow of isotonic replacement fluid 1 L/h (turnover 1 L/h)</td>
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<table>
<thead>
<tr>
<th>Experiment</th>
<th>Reservoir conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>in all experiments: total volume of 1000 mL; 600 mL of washed human erythrocytes, 100 mL of NaHCO₃</td>
</tr>
<tr>
<td>1</td>
<td>no filter priming experiment with: 100 mL of 20% human albumin, 200 mL of Ringer solution, 8 mg of moxifloxacin</td>
</tr>
<tr>
<td>2</td>
<td>filter priming for 20 min with: 100 mL of 20% human albumin, 200 mL of Ringer solution, 8 mg of moxifloxacin experiment with new reservoir: 100 mL of 20% human albumin, 200 mL of Ringer solution, 8 mg of moxifloxacin</td>
</tr>
<tr>
<td>3</td>
<td>filter priming for 20 min with: no proteins, 300 mL of Ringer solution, 8 mg of moxifloxacin experiment with new reservoir: no proteins, 300 mL of Ringer solution, 8 mg of moxifloxacin</td>
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<tr>
<td>4</td>
<td>filter priming for 20 min with: 200 mL of 20% human albumin, 100 mL of Ringer solution, 8 mg of moxifloxacin experiment with new reservoir: 200 mL of 20% human albumin, 100 mL of Ringer solution, 8 mg of moxifloxacin</td>
</tr>
<tr>
<td>5</td>
<td>filter priming for 20 min with: 100 mL of 20% human albumin, 200 mL of Ringer solution, 10 mg of moxifloxacin experiment with new reservoir: 100 mL of 20% human albumin, 200 mL of Ringer solution, 10 mg of moxifloxacin</td>
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elimination of the drug from the blood circuit ($Ca \times Qb - Cv \times Qb$; $Qb =$ blood flow rate, $Cv =$ venous serum concentration), recovery in the filtrate ($Qf \times Cf$), and descriptive statistics were performed with Excel 2002 for Windows XP.

results

Blood mixtures of the experiments had no influence on moxifloxacin stability ($1.487 \pm 0.1 \text{ mg/mL}$) compared with fresh human blood ($1.479 \pm 0.1 \text{ mg/mL}$, $P = 0.83$).

Experiment 1

The filter needed a priming time of about 20 min to achieve a stable haemofiltration situation. About 3 mg of moxifloxacin was absorbed during this run-in period (Figure 1, Table 2). The sieving coefficient was only 0.64 and the filtration clearance only 21.3 mL/min (blood flow 100 mL/min, turnover 2 L/h) (Figure 1, Table 2).

Experiment 2

Priming of the filter as before; we had stable filtration conditions and found a sieving coefficient of 0.90 and a filtration clearance of moxifloxacin of 29.9 mL/min (blood flow 100 mL/min, turnover 2 L/h) (Figure 1, Table 2).

Experiment 3

Filter priming and filtration without albumin resulted in a sieving coefficient of 1.07 and a filtration clearance of moxifloxacin of 35.7 mL/min (blood flow 100 mL/min, turnover 2 L/h) (Figure 1, Table 2).

Experiment 4

Priming of the filter and increasing the albumin concentration to 40 g/L achieved a sieving coefficient of 0.80 and a filtration clearance of moxifloxacin of 26.6 mL/min (blood flow 100 mL/min, turnover 2 L/h) (Figure 1, Table 2).

Experiment 5

Priming of the filter and decreasing the blood flow from 100 mL/min to 50 mL/min and the turnover rate from 2 L/h to 1 L/h resulted in marked reduction of the filtration clearance of moxifloxacin to 15.2 mL/min. The sieving coefficient was 0.91 (Figure 1, Table 2).
Moxifloxacin haemofiltration clearance in vitro

The recovery in the ultrafiltrate and the elimination of moxifloxacin from the blood circuit are presented in Table 2. After filter priming, the recovery of moxifloxacin in the filtrate exceeds the moxifloxacin elimination from the blood circuit in experiments 2–5.

Discussion

The clearance of moxifloxacin was unaltered in the presence of renal insufficiency following single oral doses in one study, suggesting lack of need for dose adjustment.6

Recently, Fuhrmann et al.5 indicated that the filtration clearance of 27 mL/min and the total body clearance of 318 mL/min of moxifloxacin in critically ill patients with acute renal failure undergoing CVVHDF was comparable to that in healthy subjects and patients without renal impairment.

The main findings in our study were normal moxifloxacin filtration clearances of 23–38 mL/min during CVVHDF in vitro. During CVVH, the physiological renal tubular reabsorption is lacking. Normal moxifloxacin clearance with a lower haemofiltration rate (2 L/h, about 33 mL/min) compared with the physiological glomerular filtration rate (about 100 mL/min) shows that a drug such as moxifloxacin can be excreted by CVVHDF with a similar efficiency to the normal kidney. We achieved this clearance with a turnover rate of 2 L/h (post-dilution fluid of 2 L/h and filtration rate of 2 L/h, blood flow 100 mL/min). This is in accordance with the usual standard setting during CVVHDF (blood flow ~125 mL/min, filtration rate ~1.5 L/h).3

Fuhrmann et al.5 used a continuous diafiltration method with a dialysate flow of 1 L/h and a mean turnover rate of 1 L/h (pre-dilution fluid of 1 L/h and filtration rate of 1 L/h, blood flow 150 mL/min). We found a reduced haemofiltration clearance of 15 mL/min with this filtration setting without an additional dialysis circuit. This argues for a comparable removal of moxifloxacin over the dialysate circuit with a flow of 1 L/h.

We can only speculate about the influence of the pre-dilution supply (Fuhrman study) versus our post-dilution supply. Supplying the solution before the filter is added lowers the blood viscosity but reduces the filter efficiency and increases the cost of haemofiltration, because a proportion of the generated filtrate is simply replacement fluid.4 On comparison of the filtration clearances, it appears that there is no clinically relevant difference.

The run-in experiment with the haemofilter showed a delay of about 20 min until stable filtration was achieved. Compared with the experiments after priming of the filter, an absorption of about 3 mg of moxifloxacin was achieved, which is clinically irrelevant in terms of a standard dose of 400 mg of moxifloxacin in a patient. In the filtration phase after priming in experiment 1, the Cv and the Cf concentrations exceed Ca concentrations. The cell debris in the filter during priming has obviously absorbed moxifloxacin and released it later. In experiments 2–5 after priming, the recovery of moxifloxacin in the filtrate exceeds the moxifloxacin elimination from the blood circuit. The definitive release of moxifloxacin from cell deposits into the filtrate/venous line is not clear, since we did not investigate this situation with a moxifloxacin-free reservoir after priming.

Compared with clinical reality (patients with 400 mg of moxifloxacin), in vitro haemofiltration experiments are limited because the reservoir (with a small blood volume and a small amount of a drug) has no connections to tissue compartments. Other possible factors responsible for differences in calculated sieving coefficients, based on the fraction of unbound drug in plasma versus measured sieving coefficients are: flow rates, drug concentrations, solvent systems and dilution techniques.9–11 The protein concentrations had a minor influence on the sieving coefficients and filtration clearances. These results could indicate that moxifloxacin is filtered nearly as freely as creatinine and therefore nearly independently of the blood protein concentration.12

Of other fluoroquinolones investigated (ciprofloxacin, ofloxacin, enoxacin, pefloxacin), dosage adjustment during CVVHF has been recommended only for ofloxacin based on protein-binding data in healthy volunteers and on pharmacokinetic data in patients with chronic renal failure.13 On the other hand, in a study with levofloxacin (protein binding of only 35%) during CVVH in intensive care patients it was shown that blood protein concentration had an influence on the sieving rate.14

Unfortunately, in vitro haemofiltration experiments have no predictive power for intensive care patients with a restricted hepatic function. Hepatic clearance has an important impact on the total body clearance of moxifloxacin. A main determinant of hepatic clearance of drugs is liver blood flow, which is compromised in intensive care patients with severe heart failure or septic shock.15

In conclusion, this in vitro study supports the finding5 that moxifloxacin during CVVHF with a standard turnover rate has the same filtration clearance as renal clearance in healthy volunteers and patients without renal or hepatic disease and is nearly independent of blood protein concentrations.

This confirms that 400 mg of moxifloxacin iv can be recommended once daily in anuric patients during continuous venovenous replacement therapies.5,12

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References


