Single-dose pharmacokinetics of levofloxacin during continuous veno-venous haemofiltration in critically ill patients

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The present study was performed to analyse the pharmacokinetics of levofloxacin during continuous veno-venous haemofiltration (CVVH) with a high-flux polyamide membrane. Twelve patients received 500 mg levofloxacin intravenously. The mean levofloxacin concentration peak was 1.9 ± 1.0 mg/L. The elimination half-life, haemofiltration clearance and total removal were 8.3 ± 2.6 h, 27.6 ± 8.4 mL/min and 56 ± 19%, respectively. Further multiple-dose studies are required to enable dosage recommendations to be made for patients receiving renal replacement therapy with CVVH.

Introduction

Levofloxacin is the optical \textit{S}-(−) isomer of the racemic quinolone ofloxacin. Quinolones are antimicrobial agents that are highly active against a wide variety of Gram-positive and Gram-negative bacteria and certain atypical pathogens. Levofloxacin is significantly more active than ofloxacin\textsuperscript{1,2} The \textit{in vitro} antimicrobial activity of levofloxacin is approximately two-fold greater than that of ofloxacin.\textsuperscript{3} Thus, levofloxacin can be used in the treatment of a wide variety of systemic infections.

Levofloxacin is excreted primarily unchanged by the kidney (80–86%) and undergoes limited metabolism. It is approximately 24–52% bound to serum plasma proteins, which is independent of serum drug concentration.\textsuperscript{3,4} The elimination half-life ranges between 4 and 8 h in individuals with normal renal function.\textsuperscript{1,3} Similar half-lives of ofloxacin are reported, increasing up to 19 h, in patients with renal impairment.\textsuperscript{5} During haemodialysis, the elimination half-life of ofloxacin ranges between 4 and 9 h.\textsuperscript{5}

Materials and methods

Patients

The study was performed in the intensive care unit of a teaching hospital in accordance with the guidelines of the local ethics committee. Twelve critically ill patients (two female, 10 male) with acute renal failure and suspected or proven Gram-positive or Gram-negative infection were included. Their mean age and body weight were 59.8 ± 19.2 years and 73.9 ± 15.1 kg, respectively. All patients were anuric. None of the patients received albumin substitution. Concomitant drug therapy comprised intravenous catecholamines, anticoagulation with heparin, morphine derivatives and antibiotics (vancomycin, fluconazole) other than quinolones. None of the patients had a known hypersensitivity to quinolones.

Continuous veno-venous haemofiltration (CVVH)

CVVH was performed as described previously using a high-flux polyamide capillary haemofilter with a membrane surface of 0.7 m\textsuperscript{2} (FH 66 D, Gambro, Hechingen, Germany).\textsuperscript{7} CVVH was accomplished with a roller pump (Brady BM 11, Brady, Vienna, Austria) in conjunction with an automatic balancing system (Equaline, Amicon, Ireland). Mean blood flow rate and ultrafiltration rate were 180 ± 18 and 54 ± 15 mL/min, respectively. Bicarbonate-based crystalloid solution was infused as substitution fluid to achieve a balanced fluid therapy.

Drug administration and sampling

All patients received a single dose of 500 mg levofloxacin (Hoechst-Marion-Roussel, Vienna, Austria) after initiation

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of CVVH. Levofloxacin was dissolved in 100 mL water for injection and infused over a period of 20 min into a central venous catheter different from the venous catheter used for CVVH. Blood samples were collected from the input as well as the output line of the extracorporal circuit immediately before (baseline) and at 20 min and 1, 1.5, 3, 7, 9 and 14 h after starting the infusion. Ultrafiltration samples were collected from the outlet of the ultrafiltrate compartment of the haemofilter at corresponding times. All samples were separated immediately and stored at –70°C until analysis.

**Drug assay**

The concentration of levofloxacin in serum and ultrafiltrate was determined by a high performance liquid chromatographic (HPLC) method. In short, to one part of sample two parts of acetonitrile were added and precipitated proteins were spun down at 12 000 g. To 100 μL of supernatant 300 μL distilled water was added and 25 μL was injected into the HPLC system. The HPLC system consisted of a JASCO Series 900 injector (Tokyo, Japan), pump unit and fluorescence detector. Levofloxacin was separated over a Merck RP-18 column (125 × 3 mm; Darmstadt, Germany) with a 0.5% diethanolamine/acetate buffer pH 3.5, containing 20% methanol (v/v), with a flow of 1 mL/min. For detection a fluorescence detector set at λ-ex: 277 nm and λ-em: 445 nm was chosen. The lower limit of quantification was 0.05 μg/mL serum. Intra- and interassay coefficients of variability were below 6%.

**Pharmacokinetic analysis**

The methods used for pharmacokinetic analysis have been described previously.7 Pharmacokinetic analysis was carried out for each individual patient. The sieving coefficient (Sc) was calculated as Sc = CUF/C I where C UF and C I refer to ultrafiltrate- and input serum levofloxacin concentrations, respectively. Data are presented as mean ± s.d.

**Results**

The peak levofloxacin concentrations (C max) were detected 50 min after infusion of 500 mg levofloxacin (7.1 ± 1.6 mg/kg) and were 1.9 ± 1.0 mg/L at the input port, 1.5 ± 0.9 mg/L at the output port and 1.0 ± 0.8 mg/L in the ultrafiltrate. Fourteen hours later, mean levels were 0.6 ± 0.3, 0.5 ± 0.2 and 0.3 ± 0.2 mg/L, respectively (Figure). The calculated pharmacokinetic parameters of the patients are summarized in the Table. Sc was 0.47 ± 0.27. The average total removal of levofloxacin during haemofiltration was 56 ± 19%, the mean concentration difference between the input and output port was 22 ± 9%.

**Discussion**

Levofloxacin is eliminated mainly by renal excretion, resulting in a prolonged half-life in patients with renal impairment and necessitating dosage adjustments. In healthy volunteers, mean peak plasma concentrations of levofloxacin are approximately 6.3 mg/L after an intravenous administration of 500 mg levofloxacin.8 In contrast, in this study the mean C max was 1.9 ± 1.0 mg/L after an intravenous administration of 500 mg levofloxacin.9 In contrast, this study the mean C max was 1.9 ± 1.0 mg/L after an infusion of 500 mg levofloxacin. This significant difference might be due to the fact that the intravenous administration occurred during CVVH and probably led to elevated volumes of distribution (V d) in critically ill patients [V d (healthy volunteers) 1.2 L/kg versus V d (this study) 4.3 L/kg].3 Protein binding is reported to be up to 52%, so that in consequence an adsorption to the membrane itself or binding to the secondary membrane of blood-derived protein should be considered.4 Mean elimination half-life was 8.3 ± 2.6 h compared with 6–8 h in healthy volunteers.3 CVVH removed 56 ± 19% of a single dosage of 500 mg levofloxacin. A literature search has yielded only one reference to the pharmacokinetics of levofloxacin in renal replacement therapy;9 comparisons have to be made using data on ofloxacin.

![Figure. Input (○), output (●) and ultrafiltrate (▲) concentrations of levofloxacin during CVVH after the administration of 500 mg levofloxacin intravenously.](image-url)

![Table. Pharmacokinetic data of levofloxacin in 12 study patients](table-url)
Single-dose pharmacokinetics of levofloxacin in CVVH patients

Elimination half-lives of ofloxacin ranged from 4.2 h (polysulphone membrane) to 9.9 h (cuprophane dialyser) during haemodialysis compared with 17.4/12.6 h during haemofiltration.6,10 The corresponding amounts of removal were 49.6, 21.5 and 20%, respectively. In contrast, Gisclon and co-workers’ reported a half-life of 76 h for levofloxacin in patients undergoing haemodialysis, and concluded that there was no effective removal. The differences between these results and the elimination rate of levofloxacin during this CVVH study demonstrate the great influence of membrane- and dialysis-specific factors on the clearance of a drug during renal replacement therapy.

Quinolones show concentration-dependent killing in vitro. The 24 h AUC/MIC ratio is the best predictor of bacterial killing in vivo. The peak Cmax/MIC ratio is important to prevent the emergence of resistance during treatment and a Cmax/MIC ratio of >12.2 is significantly associated with favourable clinical and microbiological responses.11 With a reported Cmax of 1.9 ± 1.0 mg/L, a Cmax/MIC ratio of >12.2 is reached for pathogens with a MIC<sub>90</sub> < 0.16 ± 0.08 mg/L, and the desired AUC/MIC ratio of >100 for pathogens with a MIC<sub>90</sub> < 0.21 ± 0.07 mg/L.

In conclusion, levofloxacin is significantly and rapidly eliminated by CVVH. Further multiple-dose studies are required to investigate serum levels when a steady state has been reached, before dosing recommendations can be made for patients receiving CVVH renal replacement therapy.

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References


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