Single-dose pharmacokinetics of fosfomycin during continuous venovenous haemofiltration

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Objectives: Dosage recommendations for fosfomycin are available for haemodialysed patients but there are no data for patients undergoing continuous renal replacement therapy. Therefore, the present study was designed to determine the concentration-versus-time profile of fosfomycin in continuous venovenous haemofiltration (CVVH).

Patients and methods: A total of 12 anuric intensive care patients (10 males and 2 females) with suspected or proven infection requiring parenteral antibiotic therapy were included in the study. All patients underwent CVVH. Blood samples were drawn from the arterial (input) and venous (output) line of the extracorporeal circuit after application of a single dose of 8 g of fosfomycin. Ultrafiltration samples were collected from the outlet of the ultrafiltrate compartment of the haemofilter. Fosfomycin in the samples was quantified by gas chromatography.

Results: The peak serum concentration was 442.7 – 124 mg/L at the arterial port. The trough serum level was 103.1 – 36.6 mg/L at the arterial port after 720 min. The mean value of the area under the concentration-versus-time curve from 0 to 12 h (AUC0–12) was 2159.4 – 609.8 mg·h/L. Mean total removal of the drug was 76.7 – 6.2%. The mean calculated clearance was 1.1 – 0.2 L/h for CLHF. Mean CLtot was 6.4 – 7.7 L/h.

Conclusions: A regimen of 8.0 g of fosfomycin every 12 h, which is usually used in patients with intact renal function, should be an appropriate antimicrobial treatment for patients undergoing CVVH.

Keywords: bactericidal agents, antibiotic agents, renal replacement therapy

Introduction

Fosfomycin is a bactericidal broad-spectrum antibiotic that is not structurally related to other classes of antimicrobial agents. High in vitro activity against Gram-positive pathogens such as Staphylococcus aureus and Gram-negative bacteria such as Pseudomonas aeruginosa has been proven in several studies. Frossard et al. demonstrated that fosfomycin concentrations in plasma and soft tissue suggest a high degree of tissue penetration. These promising qualities have made the substance an often employed antibiotic in critically ill patients with severe infections or sepsis but no data are available about fosfomycin pharmacokinetics in patients under continuous venovenous haemofiltration (CVVH).

CVVH is an important supportive extracorporeal renal replacement therapy in the treatment of intensive care patients suffering from sepsis and systemic inflammatory response syndrome. Physicochemical properties of the drug (protein-binding, volume of distribution, molecular charge, molecular weight) and characteristics of the renal replacement technique used (type of filter, blood flow rate, usage of counter-current dialysis, ultrafiltration rate, adsorption of the drug onto the filter) are the determining factors of renal replacement therapy. However, dosage recommendations for fosfomycin are available for haemodialysed patients but there are no data for patients undergoing continuous renal replacement therapy.

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knowledge of concentrations of antimicrobial agents in patients undergoing CVVH is crucial for dosage recommendations in patients suffering from severe infections since underdosing might result in therapeutic failure and fatal outcome. Therefore, the present study was designed to determine the concentration-versus-time profile of fosfomycin in CVVH.

Patients and methods

Patients

A total of 12 anuric intensive care patients (10 males and 2 females) with a mean age of 68 ± 8 years with suspected or proven infection requiring parenteral antibiotic therapy were included in the study. Demographic characteristics are presented in Table 1. Mean serum creatinine level was 264 ± 97 μmol/L prior to CVVH. Haemodialysis was not employed during the study. Concomitant drug therapy consisted mainly of intravenous (iv) catecholamines, anticoagulation with heparin, morphine derivates and sucralfate. None of the patients received albumin substitution. Additional antimicrobial therapy and antimycotic therapy were permitted.

All drugs were administered as clinically indicated by the attending physician. None of the patients was hypersensitive to fosfomycin or showed other intolerance to this substance. The protocol was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki (1964) and current revisions of Good Clinical Practice Guidelines of the European Commission and the Austrian Drug Law (AMG). The study met the criteria set forth by the local ethics committee for patients who were unable to give written consent because they were sedated or comatose.

CVVH

CVVH was performed as described previously using a polyethylene sulfone haemofilter with a membrane surface of 1.2 m² (Aqua Max HF 12, Fresenius, Germany). CVVH was accomplished with a roller pump (Brady, Vienna, Austria) in connection with an automatic balancing system (Equaline, Amicon, Ireland). The artificial kidneys (dialysis membranes) were functional during the whole blood sampling period. The dialysis membranes were not changed during the sampling time. The standard blood flow rate was 180 mL/min; rates were adjusted according to clinical need. The ultrafiltration rate was 25 mL/min. Bicarbonate-based crystalloid solution was infused as substitution fluid into the venous line (post-dilution) at a rate that depended on balanced fluid therapy.

Drug administration and sampling

All patients received a single dose of 8.0 g of fosfomycin dry powder (Biochemie, Kundl, Austria), reconstituted with 200 mL of sterile water over a period of 30 min into a central venous catheter, different from the venous catheter used for CVVH. Blood samples were drawn from the arterial (input) and venous (output) line of the extracorporeal circuit before and 15, 30, 60, 90, 180, 360, 480 and 720 min after the start of 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 –80°C until analysis.

Drug assay

Fosfomycin in the samples was quantified by gas chromatography after derivatization with bis-(trimethylsilyl)-trifluoracetamide and detection with a nitrogen–phosphorus detector. Fosfomycin disodium salt was a gift from Biochemie GmbH, Kundl. Ethylphosphonic acid (internal standard, Aldrich 28,987-6), N,O-Bis-(trimethylsilyl)-trifluoracetamide with 1% trimethylchlorosilane (BSTFA + 1% TMCS, Fluka 15238), methanol (chromasolv grade, Riedel-de Haen 34860) and pyridine (p.a., Fluka 82702) were obtained through Sigma-Aldrich Co., Vienna. An Eppendorf centrifuge 5415 C was used for centrifugation at room temperature, and for drying under reduced pressure a Heto VR1 centrifuge was used. Stock solutions of fosfomycin and ethylphosphonic acid were prepared in methanol and stored at 4°C. Derivatization was performed with a mixture of one part of BSTFA + 1% TMCS and three parts of pyridine in an Eppendorf thermostat 3401 using standard 1.5 mL Eppendorf vials. Samples were transported on dry ice to the laboratory and stored at –70°C until analysis.

After thawing at room temperature 100 μL of sample was mixed with 400 μL of methanol containing 125 μg/mL ethylphosphonic acid as the internal standard and centrifuged for 5 min at 16,000 g. From the supernatant 100 μL was transferred to another vial and dried under reduced pressure. Silylation was conducted by incubation of the dried residue for 15 min at 56°C with 50 μL of the above 1:3 mixture of BSTFA + 1% TMCS and pyridine. The solution was transferred to an autosampler vial with 100 μL inserts and 1 μL was injected in split mode.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Apache score</th>
<th>Diagnosis</th>
<th>Microbiological finding</th>
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<tr>
<td>1</td>
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<td>69</td>
<td>176</td>
<td>83</td>
<td>33</td>
<td>CAP</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>W</td>
<td>67</td>
<td>153</td>
<td>64</td>
<td>40</td>
<td>septic shock</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>82</td>
<td>170</td>
<td>98</td>
<td>40</td>
<td>aortic aneurysm</td>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td>4</td>
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<td>67</td>
<td>168</td>
<td>68</td>
<td>42</td>
<td>CAP, septic shock</td>
<td>Staphylococcus aureus</td>
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<tr>
<td>5</td>
<td>M</td>
<td>63</td>
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<td>84</td>
<td>34</td>
<td>peritonitis</td>
<td>S. aureus</td>
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<tr>
<td>6</td>
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<td>61</td>
<td>182</td>
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<td>43</td>
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<td></td>
</tr>
<tr>
<td>7</td>
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<td>64</td>
<td>170</td>
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<td>38</td>
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<tr>
<td>8</td>
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<td>64</td>
<td>165</td>
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<td>9</td>
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<td>79</td>
<td>176</td>
<td>79</td>
<td>34</td>
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<tr>
<td>10</td>
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<td>79</td>
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<td>64</td>
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<tr>
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<td>93</td>
<td>42</td>
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<td>W</td>
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<td>165</td>
<td>83</td>
<td>38</td>
<td>endocarditis</td>
<td>Streptococcus mitis</td>
</tr>
</tbody>
</table>

M, male; F, female; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease.
For the determination of fosfomycin a Hewlett Packard 5890 Series II gas chromatograph equipped with a nitrogen–phosphorus detector and a Hewlett Packard 7673 autosampler and a Restek Rtx-5 capillary column (5% diphenyl–95% dimethylpolysiloxane, 30 m × 0.53 mm i.d., film thickness 1.5 μm) was used. Helium was used as the carrier gas. The pressure was set at 35 kPa for the Rtx-5 through the split injector. Gas flows for the detector were set according to the manual. The nitrogen–phosphorus detector potential was set to a baseline value of 25 pA. A temperature gradient of 30°C/min starting from 100°C to a final temperature of 170°C was used. Data acquisition was performed using the Hewlett Packard 3396 Series II integrator and a Hewlett Packard 7673 controller.

Chromatograms of blank samples did not show interfering peaks. After a pre-study validation fosfomycin was quantified with daily calibration curves of the ratio between analyte and internal standard from blank matrix samples spiked with concentrations from 6 to 480 mg/L. For the quality control samples of 60 mg/L an inter-day reproducibility of 15.4% with an accuracy of 97.9% was found and for quality control samples spiked with 240 mg/L an inter-day reproducibility of 9.7% together with an accuracy of 97.2% was found.

Pharmacokinetic analysis

The methods of pharmacokinetic analysis using commercially available software (Kinetica 3.0, Innaphase Philadelphia, USA) have been described recently. In brief, an open one-compartment model was applied. Statistical analysis was performed using a commercially available computer program (Statistica, StatSoft Inc., Tulsa, USA). All data are presented as means ± SD. The area under the concentration–time curve (AUC) was determined by the trapezoidal rule. The elimination half-life was calculated by \( t_{1/2} = \ln 2/k_e \). The serum drug concentrations at the peak (30 min after the start of the drug infusion) and at the trough of the first dosing interval, respectively.

Table 3. Mean pharmacokinetic parameters of fosfomycin following a single iv dose of 8.0 g during haemofiltration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Result</th>
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<tbody>
<tr>
<td>( C_{\text{amin}} )</td>
<td>mg/L</td>
<td>442.7 ± 124</td>
</tr>
<tr>
<td>( C_{\text{amin}} )</td>
<td>mg/L</td>
<td>103.1 ± 36.6</td>
</tr>
<tr>
<td>S</td>
<td>%</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>CLHF</td>
<td>L/h</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Retot</td>
<td>%</td>
<td>76.7 ± 6.2</td>
</tr>
</tbody>
</table>

For the pharmacokinetics of fosfomycin measured in the arterial circulation during haemofiltration are presented in Tables 2 and 3.

Twelve patients received 8.0 g of fosfomycin intravenously. The peak serum concentration was 442.7 ± 124 mg/L at the arterial port. The trough serum level was 102.1 ± 36.5 mg/L at the arterial port after 720 min. The mean arterial half-life was 12.1 ± 5.2 h. The mean value of the area under the concentration-versus-time curve from 0 to 12 h (AUC_0–12) was 2159.4 ± 609.8 mg·h/L. The sieving coefficient was 0.7 ± 0.1. Mean total removal of the drug was 76.7 ± 6.2%. The calculated clearance was 1.1 ± 0.2 L/h for CLHF. The CLtot was 6.4 ± 7.6 L/h. The time versus concentration profile of fosfomycin in the arterial, venous and ultrafiltrate circulation is shown in Figure 1.
Arterial to serum levels found in critically ill patients without renal failure undergoing continuous venovenous hemofiltration (CVVH) is usually performed in intensive care units if patients are in need of renal replacement therapy. It is an important option in supportive treatment because of its good haemodynamic tolerance.

Fosfomycin remains the single representative of the epoxide family of antimicrobial drugs. Fosfomycin has an extremely low tolerance.

Data on the pharmacokinetics of fosfomycin, which has a renal elimination of 95%, exist for haemodialysed patients, but not for patients undergoing CVVH. The aim of the present study was to evaluate the pharmacokinetics of fosfomycin in critically ill patients with renal failure undergoing continuous renal replacement therapy.

All patients tolerated the iv infusion of 8.0 g of fosfomycin without apparent side effects. Peak and trough levels were similar to serum levels found in critically ill patients without renal replacement therapy and healthy volunteers.

We observed a longer mean half-life than found in intensive care patients without renal replacement therapy.

Optimal bacterial eradication by fosfomycin will be achieved when the time period exceeding the MIC for the relevant pathogen (t > MIC) is maximized. Optimal effectiveness can be expected from the first antibiotic dosage when the target’s MIC is covered for at least 60–70% of the dosing interval. As indicated by Figure 1, pathogens with an MIC up to 64 mg/L should be inhibited by 8.0 g fosfomycin administered every 12 h to patients undergoing CVVH (Figure 1). Also serum trough levels exceeded the concentration of 64 mg/L throughout the duration of antimicrobial treatment.

In conclusion a regimen of 8.0 g of fosfomycin every 12 h should be an appropriate antimicrobial treatment for patients undergoing CVVH and suffering from an infection caused by a fosfomycin-susceptible pathogen.

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Transparency declarations

None to declare.

References

Single-dose pharmacokinetics of fosfomycin


