Extracellular concentrations of fosfomycin in lung tissue of septic patients

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Objectives: The present investigation explored the ability of fosfomycin to penetrate lung tissue of septic patients by utilizing the microdialysis technique.

Methods: After microdialysis probe insertion into healthy and infected lung tissue, a single intravenous dose of 4 g of fosfomycin was administered.

Results: The mean $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{0-4}$ and $AUC_{0-1}$ for healthy lung were $131.6 \pm 110.6$ mg/L, $1.1 \pm 0.4$ h, $242.4 \pm 101.6$ mg.h/L and $367.6 \pm 111.9$ mg.h/L, respectively. The corresponding values for infected lung were $107.5 \pm 60.2$ mg/L, $1.4 \pm 0.5$ h, $203.5 \pm 118.4$ mg.h/L and $315.1 \pm 151.2$ mg.h/L. The half-life of fosfomycin ranged from 2.2 to 2.7 h between compartments. The magnitude of lung tissue penetration, as determined by the ratios of the $AUC_{0-\infty}$ for lung to the $AUC_{0-\infty}$ for plasma, was $0.63 \pm 0.31$ and $0.53 \pm 0.31$ for healthy and infected lung, respectively.

Conclusions: We conclude that fosfomycin achieves antimicrobially effective concentrations in infected lung tissue.

Keywords: tissue, penetration, human, microdialysis

Introduction

Previous studies investigating interstitial levels of fosfomycin in adipose soft tissue, skeletal muscle tissue or cerebrospinal fluid were performed in diabetic patients and in critically ill subjects.1–4 Other studies examined the concentrations of fosfomycin in the interstitial space fluid of healthy, unaffected soft tissue in healthy men.5 From these studies, we learned that concentrations of fosfomycin in unaffected and infected soft tissues or bone are sufficiently high to kill relevant bacteria.1–5 Another important finding was that interstitial tissue levels of fosfomycin were largely comparable to corresponding free concentrations in plasma or serum.

Hence, the pharmacokinetic profile of fosfomycin is excellently described for many tissues and clinical conditions except for lung tissue. Against this background, the ability of fosfomycin to penetrate into human pulmonary tissue is still controversial. Therefore, the present investigation aimed to address this important clinical question, particularly at times of increasing resistance rates of bacteria to traditional anti-methicillin-resistant Staphylococcus aureus (MRSA) and anti-extended-spectrum β-lactamase (ESBL) agents. Intravenous fosfomycin is frequently used in Austria, Brazil, France, Germany, Spain, South Africa and Japan for the therapy of severe and life-threatening Gram-positive infections and was recently reported to be a therapeutic option in the therapy of MRSA and ESBL-producing Enterobacteriaceae infections.6

Methods

The study was approved by the Ethics Committee of the Medical University of Graz, Austria. All patients were given a detailed description of the study and their written informed consent was obtained prior to the start of study-related procedures. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the European Commission.

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Patients

Sepsis was diagnosed according to the criteria from the American College of Chest Physician/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee.\textsuperscript{7} Conservative treatment options failed to work well in all patients scheduled for surgical intervention. In these subjects, lateral thoracotomy, decortication, debridement and pulmonary wedge resection in the case of lung abscess were considered the treatments of choice.

Measurement of interstitial fosfomycin concentrations and chemical analysis

The principles of microdialysis are described in detail elsewhere.\textsuperscript{6} After a 20 min equilibration period, a single dose of 4 g of fosfomycin (Fosfomycin Sandoz\textsuperscript{TM}; Sandoz, Kundl, Austria) was administered to the patient intravenously over ≈30 min. Microdialysates and plasma aliquots collected from venous blood after centrifugation at 1600 g for 10 min were stored at approximately −70°C until analysis.

Fosfomycin concentrations in specimens were determined by the use of a previously published and modified method using capillary gas chromatography with nitrogen phosphorous detection following derivatization with N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTFA).\textsuperscript{9} The limit of quantification for fosfomycin was 1 mg/L. The intra-day and inter-day coefficients of variation were <0.07.

Pharmacokinetic calculations

Non-compartmental pharmacokinetic analysis was employed for the calculation of missing data points. The main pharmacokinetic parameters such as half-life at the β-phase (T1/2β), peak concentration (C\textsubscript{max}), time to reach peak concentration (T\textsubscript{max}) and the area under the concentration-versus-time curves from time zero to \(\infty\) (AUC\textsubscript{0–\infty}) were calculated by use of the linear trapezoidal rule. Commercially available computer software (Kinetica\textsuperscript{TM}, version 4.4.1; Thermo Electron Corporation, Waltham, MA, USA) was employed.

Results and discussion

In total, eight patients (five males and three females) were studied in the present investigation. The pharmacokinetic profile of one subject was not eligible for further evaluation, because of malfunction of microdialysis probes. The mean age was 58.7 years (range 26–80). Subjects had a mean body weight of 74.3 kg (range 60–90) and a mean body mass index of 24 kg/m\textsuperscript{2} (range 21–28).

Mean values of C\textsubscript{max}, T\textsubscript{max} and AUC\textsubscript{0–\infty} for healthy lung were 131.6 ± 110.6 mg/L, 1.1 ± 0.4 h and 367.6 ± 111.9 mg·h/L, respectively, after administration of a single intravenous dose of 4 g of fosfomycin. The corresponding values for infected lung were 107.5 ± 60.2 mg/L, 1.4 ± 0.5 h and 315.1 ± 151.2 mg·h/L. The half-life of fosfomycin varied from 2.2 to 2.7 h between compartments. The degree of lung tissue penetration, as determined by the ratio of the AUC\textsubscript{0–\infty} for lung to the AUC\textsubscript{0–\infty} for plasma, was 0.53 ± 0.31 and 0.63 ± 0.31 for infected and healthy tissue, respectively. Fosfomycin was well tolerated in all subjects. No adverse events related to the study drug or to microdialysis probe insertion were observed.

In the present study, we were able to show that fosfomycin penetrates well into the interstitial space fluid of healthy and infected lung tissue in patients scheduled to undergo elective thoracotomy due to severe complications of bacterial pneumonia. The concentration-versus-time profiles of fosfomycin in plasma, infected lung tissue and healthy lung tissue are depicted in Figure 1. The main pharmacokinetic parameters are summarized in Table 1. Thus, severe inflammation exerted no clinically relevant effect on the ability of fosfomycin to penetrate into infected lung tissue (Figure 1), i.e. a finding that is consistent with reported data from previous investigations in patients presenting either with severe sepsis, cellulitis, deep seated infections, diabetic foot syndrome and bacterial osteomyelitis, or cerebral infections.\textsuperscript{1–5,10} Hence, we provide strong evidence that free fosfomycin in plasma equilibrates almost completely with the extracellular space fluid of tissues under inflammatory and normal conditions (Figure 1). The reasons for the ability of fosfomycin to penetrate into the interstitium of tissues are not yet fully understood, but may be partly related to its high hydrophilicity, small molecular weight of only 138 g/mol and negligible plasma protein binding.\textsuperscript{6}

From previous pharmacokinetic/pharmacodynamic experiments, we learned that effective bacterial killing for ‘time-dependent antibiotics’ such as fosfomycin, may be expected when the MIC for the pathogen is exceeded for at least 40% of the dosing interval.\textsuperscript{1,11} With regard to the relatively low dose of 4 g applied in the present study and considering our pharmacokinetic/pharmacodynamic calculations (Table 2), these data show that this criterion is met for infected and healthy lung tissue for MICs of up to 32 mg/L. However, there was considerable inter-subject variability in tissue and plasma pharmacokinetic profiles, exposing individual subjects to the potential risk of under-dosing. Such patients may require optimization of fosfomycin’s dosing regimen, where shorter dosing intervals or higher doses of up to 8 g of fosfomycin given two or three times a day should be considered as an alternative, if subjects present with severe infection and have a creatinine clearance of >40 mL/min. Total daily doses of 24 g of fosfomycin are approved for the therapy of severe and life-threatening infections in Austria, Germany, Spain, France and elsewhere in the European Union. This dosing regimen will cover pathogens for which the MIC is

![Figure 1. Mean pharmacokinetic profiles of fosfomycin in plasma, infected lung tissue and healthy lung tissue in eight patients after single intravenous administration of 4.0 g. Error bars are standard deviations. Horizontal lines indicate different MICs ranging from 8 to 32 mg/L.](image-url)
32 mg/L for periods much longer than 40% of the dosing interval in most subjects.

The potential for the development of resistance to fosfomycin after mono-therapeutic use is an important limitation. Fosfomycin given at total daily doses of up 24 g may be linked to increased sodium load and could lead to oedema and augmented potassium excretion necessitating its replacement. On rare occasions allergic reactions may be observed. Headache, loss of appetite, thrombophlebitis, visual impairment, nausea and other clinically less relevant untoward effects may also occur.6

In summary, we demonstrated that the free concentration-versus-time profile of fosfomycin in the interstitium of infected lung tissue mimics closely the pharmacokinetic profiles determined in plasma and healthy lung tissue indicating that fosfomycin penetrates infected lung tissue effectively.

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Transparency declarations

S. A. K. is an employee of J&P MEDICAL RESEARCH LTD, which is an international independent research institute basically operating according to the Public–Private-Partnership concept. C. J. is managing director of J&P MEDICAL RESEARCH Ltd, owns 100% options, and is also a consultant for pharmaceutical companies. All other authors declare having no relationship with companies that make products relevant to the manuscript and have no conflicts of interest with the present work.

References

