Extracellular concentrations of fosfomycin in lung tissue of septic patients.

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OBJECTIVE: Fosfomycin (FOM), a broad-spectrum antibiotic agent, is widely used in distinct EU-member states for the therapy of severe infections including those associated with methicillin-resistant or methicillin-sensitive *Staphylococcus aureus* (MRSA, MSSA) or extended-spectrum beta-lactamase (ESBL) producing bacteria. In light of increasing resistance rates of MSSA, MRSA and ESBL producing bacteria against traditional anti-staphylococcal and anti-ESBL antibiotics, we carried out the present investigation and explored FOM´s ability to penetrate human lung tissue. PATIENTS AND METHODS: Extracellular concentrations of FOM in lung tissue of eight patients scheduled to undergo elective lung surgery due to severe pulmonary infection were investigated. Plasma and healthy lung served as reference tissues. RESULTS: After a single intravenous dose of 4 g of FOM, the mean C_{max}, T_{max}, AUC_{0-4} and $AUC_{0-infinitum}$ for healthy lung were 131.6 ± 110.6 mg/L, 1.1 ± 0.4 h, 242.4 ± 101.6 mg*h/L and 367.6 ± 111.9 mg*h/L, respectively. The corresponding values for infected lung were 107.5 ± 60.2 mg/L, 1.4 ± 0.5 h, 203.5 ± 118.4 mg*h/L and 315.1 ± 151.2 mg*h/L. FOM´s half-lives ranged from 2.2 to 2.7 h between compartments. The magnitude of lung tissue penetration, as determined by the ratios of the $AUC_{0-infinitum}$ for lung to the $AUC_{0-infinitum}$ for plasma, was 0.63 ± 0.31 and 0.53 ± 0.31 for healthy and infected lung, respectively. CONCLUSION: Based on pharmacokinetic-pharmacodynamic (PK-PD) calculations derived from lung tissue and plasma, we conclude that FOM may be considered an effective antibiotic for the treatment of severe lung infections caused by problematic pathogens like MSSA, MRSA and ESBL producing strains. However, clinically well tolerated doses of up to 8 g of FOM given 2-3 times a day may be necessary in some individuals to account for large inter-subject differences in tissue- and plasma pharmacokinetic profiles of FOM in patients suffering from severe infections and sepsis.

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. Other studies examined the concentrations of fosfomycin in the interstitial space fluid of healthy, unaffected soft tissue in healthy men. From these studies, we learned that concentrations of fosfomycin in unaffected and infected soft tissues or bone are sufficiently high to kill relevant bacteria. 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 b-lactamase (ESBL) agents. Intravenous fosfomycin is frequently used in Austria, Brazil, France, Germany, Spain, South Africa and Japan for the herapy of severe and life-threatening Gram-positive infections nd was recently reported to be a therapeutic option in the herapy of MRSA and ESBL-producing Enterobacteriaceae Infections.