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An evaluation of the effectivity of the current treatment of uncomplicated urinary tract infections with fosfomycin based on urinary concentrations in healthy volunteers

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Background:

In an era of emerging drug resistance and lack of new antibiotics, old antibiotics, such as fosfomycin, are increasingly being prescribed to patients. Surprisingly, little is known of the urinary concentrations of fosfomycin after a single, oral dose of 3 grams. In the current study, we aimed to gain more insight in the pharmacokinetics of fosfomycin to evaluate the effectivity of the treatment of uncomplicated urinary tract infections with fosfomycin. Effectivity is based on urine concentrations in healthy volunteers and the target concentrations to cover the most common uropathogen, *E. coli.*

Material/methods:

28 healthy, female volunteers were included. After intake of 3 grams fosfomycin trometamol, urine samples were collected during the following 48 hours with every voiding and twice daily from 48 hours to 7 days. The time, volume and pH of each sample were noted and fluid intake was recorded. The fosfomycin concentrations in the urine samples were quantified with a validated ultra-performance liquid chromatography – tandem mass spectrometer (UPLC-MS/MS) system. The creatinine clearance was estimated with the Crockcroft-Gault equation based on the serum creatinine. The time above the MIC's in urine was calculated based on the concentration-time curves of each volunteer for a range of 0.5 to128 mg/L.

Results:

A total of 680 urine samples were collected. The following mean values of the pharmacokinetic parameters in urine were calculated, wherein a high inter-individual variability was found: peak concentration 2050.3 ± 1095.8 mg/L; time of the peak 7.5 ± 4.3 h; concentration half-life 12.2 ± 6.4 h and fosfomycin clearance 30.2 ± 6.9 mg/h. In total, an average of 1415.3 ± 301.7 grams was excreted; the urinary recovery was 47 ± 10.1% and 95% of this total amount was excreted within 42 hours of which the main part was excreted during the first 6 hours. An exponential relationship was found between the cumulative fosfomycin excretion over time. Concentrations remained above 64 mg/L for at least 51 hours in all patients and > 128 mg/L for 39 hours. Covariate analysis indicated that a small reduction in creatinine clearance (80 mL/min compared with a mean of 121 mL/min) and a urination frequency of more than 15 in 48 hours, were associated with a reduced T>MIC.

Conclusions:

We found a relationship between the creatinine clearance as well as the number of urinations with the time of urinary fosfomycin above MIC. A considerable inter-individual variability was observed in the pharmacokinetics of fosfomycin indicating potential underexposure in part of the population and the necessity to reevaluate the current dosing regimen of 3 grams.