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Oral calcium fosfomycin: Pharmacokinetic/pharmacodynamic study

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1. Introduction

Urinary tract infections (UTIs) are some of the most common bacterial infections, affecting 150 million people each year worldwide. Calcium fosfomycin is an antimicrobial agent with indication for the treatment of uncomplicated UTIs, being *Escherichia coli* the most frequently isolated microorganism [1, 2]. EUCAST clinical breakpoint of oral fosfomycin for *E. coli* in uncomplicated UTI is 8 mg/L, and the epidemiologic cutoff (ECOFF) for E. coli is 4 mg/L [3]. Urinary drug concentrations are correlated with antibacterial activity in uncomplicated UTI infections. Indeed, high urinary antimicrobial concentrations are essential for efficacy.

Therefore, the objective of this study was to analyze the urine concentrations of fosfomycin after oral administration to healthy women at different dosing levels from a pharmacokinetic/pharmacodynamic (PK/PD) point of view.

2. Materials and methods

Urine data come from an open-label, randomized, crossover study of bioavailability of various doses of Fosfocina® (Laboratorios ERN, S.A.) and formulations in healthy women under fasting conditions, carried out in the Unidad de Ensayos Clínicos (Hospital Universitario de Álava, Vitoria-Gasteiz, Spain). The study was approved by the Ethics Committee for Investigation with medicinal products of Euskadi. The authorization of the AEMPS was also obtained (Code: PD7522.22, EudraCT: 2020-001664-28).

The volunteers received oral calcium fosfomycin as a single dose of 500 mg (capsule), a single dose of 1000 mg (capsule or suspension), and a multiple dose of 1000 mg q8h for three days (capsule). Urine samples were collected over a period of 36 hours.

From the concentrations of fosfomycin in urine, the area under the urine concentration-time curve over a period of 24 h (AUC24) was calculated by the trapezoidal rule. The AUC24/MIC > 24 was considered the PK/PD target [4]. Monte Carlo simulations were used to estimate the cumulative fraction of response (CFR), defined as the expected population probability of target attainment for a specific antimicrobial dose and a specific population of microorganisms. CFR is understood as the expected probability of success of the therapy. MIC distribution of E. coli against fosfomycin reported by EUCAST was used [3]. A 10.000-subject simulation was used with Oracle® Crystal Ball.

3. Results

Figure 1 shows a comparison of the mean urine

profiles in all groups. As the figure shows, mean concentration of fosfomycin in urine, even at the lowest dose level, is above 32 mg/L for at least 24 hours with all evaluated formulations.

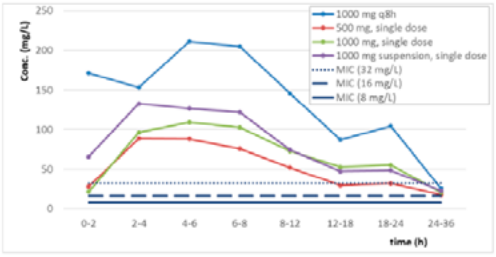

Fig 1. Mean urine concentration of fosfomycin compared to MIC of 8, 16 and 32 mg/L.

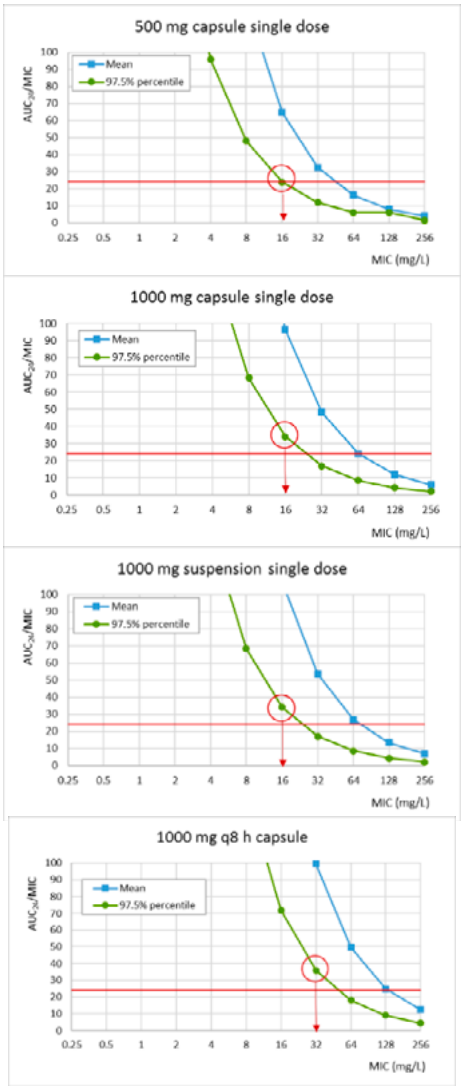

Fig. 2. AUC24/MIC values vs MIC for all dose levels.

Figure 2 shows the AUC24/MIC values for a range of MIC values (expressed as mean and 97.5 % percentile). PK/PD breakpoints can be read directly from the graphic at the intersection of the horizontal line at the PK/PD target (AUC24/MIC > 24) and the 97.5 % percentile curve.

Table 1 summarizes the PK/PD breakpoints (highest MIC value with a probability of target attainment ≥ 90 %) of fosfomycin at the different dose levels and dosage form, and the values of CFR against E.coli considering the MIC profile reported by EUCAST [3].

Table 1. PK/PD breakpoints (non-species related) of fosfomycin and CFR against E. coli.

Dose/formulation	PK/PD (mg/L)	CFR (%)
500 mg capsule, sd	16	96
1000 mg capsule, sd	16	96
1000 mg suspension, sd	16	96
1000 mg q8h capsule	32	97

4. Conclusions

Urine exposition of fosfomycin greatly exceeds the EUCAST clinical and ECOFF breakpoint of E. coli. MIC value supposedly covered with 500 mg capsule single dose, with 1000 mg capsule single dose, and with 1000 mg suspension single dose is 16 mg/L. In the same way, the MIC value supposedly covered with 1000 mg q8h capsule is 32 mg/L; therefore, this is the best option. Based on PK/PD analysis from urine concentrations, empiric treatment of uncomplicated UTI with oral calcium fosfomycin provides a high probability of treatment success (> 95 %).

Acknowledgments

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