Methods

Study design and subjects: Urine from six healthy volunteers [7] was collected before and following an oral dose of 800mg FIN according to the following time intervals: 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, and 24 to 48 hours. Urine for 1 to 4 hours was then pooled for bactericidal time determination. Absence of antibacterial activity in pooled urine was shown by the lack of inhibition of bacterial growth.

Drug concentrations in urine: The concentration of FIN in urine samples was measured by HPLC and tandem (MS/MS) mass spectrometry using a concentration range of 0.010 – 50.000 mg/L.

Determination of MIC: Minimal inhibitory concentrations (MICs) of FIN, levofloxacin (LVX) and ciprofloxacin (CIP) were determined by both microbroth procedures according to the CLSI at pH 5.8, 7.2 and 8.0. MICs were also determined in synthetic urine medium, pH 5.5.

Determination of UBTx and AUBT*: Two-fold serial dilutions of urine samples were prepared in antibiotic-free urine and used to prepare a microbroth test with an inoculum of 5 × 10⁴ to 5 × 10⁵ CFU/mL. Bactericidal activity in urine was determined by plating 10 µL of each well onto fresh agar. Urinary bactericidal data (UBT; %) were calculated as the reciprocal value of the highest dilution to produce a >99.9% (>3 × 10⁹ CFU/mL) reduction of the initial inoculum. The area under the UBT-time curve (AUBT) was calculated as the sum of the products of the UBTs and the respective time intervals for 24h post-dosing for each test organism and drug. Data analysis has been described previously [8].

Results and Discussion

Urine pharmacokinetics

Urinary pharmacokinetics and results following 800mg dose are summarized in Table 1. FIN reached mean peak levels of 150 mg/L in urine collected between 4 – 8 h. The peak levels of FIN were not different between the different test organisms. The urinary AUC/Cl values for FIN were highly correlated with the MICs of FIN for each test strain [9]. This corresponded with the urinary concentration-time profiles of FIN (Table 3).

Conclusion

FIN exhibited superior antibacterial activity to CIP and LVX in synthetic urine samples against a panel of UTI pathogens. FIN was well tolerated in six healthy volunteers receiving a single 800mg dose and reached a mean peak urinary concentration of 150 mg/L.

FIN remained above the MIC for the tested strains except those with an MIC in synthetic urine of ≤32 mg/L, in the urine for 4h post-dosing.

This corresponded with the urinary bactericidal activity of FIN, demonstrated by positive UBT and AUBT*, against these strains.

Urinary bactericidal activity

Urinary bactericidal data (UBT; %) of FIN in native, synthetic (pH 5.5) and alkaline (pH 8.0) urine, from the initial period after dosing (UBT0-1h) and in urine sampled 12 – 24h after dosing (UBT12-24h) is shown in Table 1.