POPULATION PHARMACOKINETICS OF MICAFUNGIN IN PLASMA AND BURN ESCHAR IN SEVERELY BURNED CRITICALLY ILL PATIENTS

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Background:

Fungal infections are a leading cause of burn wound infections, with *Candida* spp. the most frequent pathogen.

Micafungin exhibits a potent antifungal activity against most clinically important *Candida* species, but there is limited information about its pharmacokinetics in patients with severe burn injuries.

The **aim of this study** was to describe the pharmacokinetics of micafungin in plasma and burn eschar in critically-ill patients with severe burn injuries.

Materials and methods:

Patients received 100-150mg/day of micafungin for a proven or suspected fungal infection.

Serial plasma and burn eschar tissue samples were collected at serial time points. Micafungin concentrations in plasma and eschar homogenate were determined by HPLC. The concentration-time data were analyzed using a population pharmacokinetic approach with Pmetrics ®.

Results:

Fifteen patients were included: 12 (80%) male, median (range) age, SOFA and total body surface area burned (TBSA) were 43 (18-77) years, 12 (1-12) points and 50 (23-80)%, respectively.

On day 1, the median (IQR) of $AUC_{0\text{-}24h}$ in plasma was 48.3 (37.7-55.8) mg.h/L and in burn eschar 3.8 (3.3-17.4) mg.h/L, which corresponded to a median eschar/plasma ratio of 0.15 (0.06-0.38).

Micafungin concentrations in plasma at the end of the infusion (peak) on day 1 and 4 were inversely correlated with the % burned TBSA (Spearman's rho = -0.539 (P = .04) and Spearman's rho = -0.750 (P = .01), respectively). The time-course of plasma and eschar homogenate micafungin concentrations was best described by a three-compartment linear model.

The mean (SD) estimates for clearance, volume of distribution of the central compartment, the rate constant for drug distribution from the central to peripheral compartment and the rate constant for drug distribution from the peripheral to central compartment were 1.61 (0.62) L/h, 6.07 (2.77) L, 16.87 (11.93) h^{-1} and 9.93 (6.02) h^{-1}, respectively.

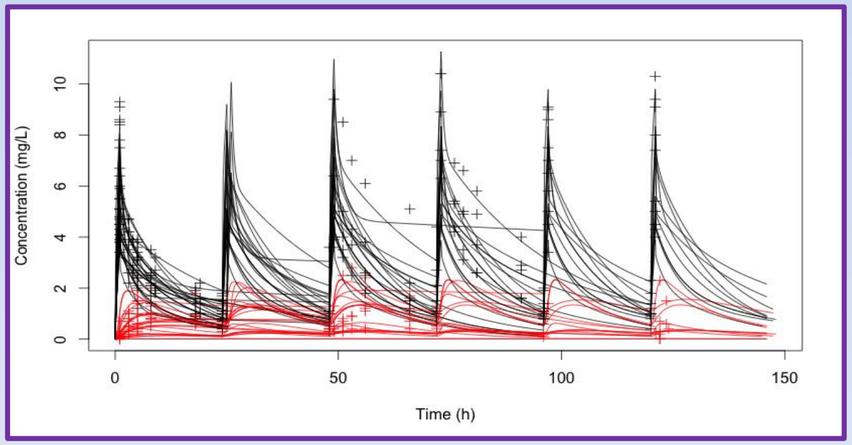

Figure 1. Observed micafungin concentrations in plasma (black symbols) and tissue fluid (red symbols). Posterior predictions of the concentration-time curve for plasma (black) and tissue fluid (red) are denoted with solid lines (n=25).

Conclusions:

This is the first population pharmacokinetic study of micafungin in severely burned patients. Micafungin showed low, but highly variable penetration into the burn eschars. These results suggest the need to consider the administration of higher doses of micafungin in severely burned patients along with a potential value for dose optimization using therapeutic drug monitoring to ensure target concentrations are achieved.

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