Pharmacokinetic modelling to predict the metabolic saturation of voriconazole in paediatrics with life-threatening invasive fungal infections Jelien den Hollander, Ron Keizer, Tony Lai, Thi Nguyen, Sophie Stocker, Jan-Willem Alffenaar; Sydney School of Pharmacy, Faculty of Medicine and Health, The University of Sydney

Introduction: Voriconazole is a drug used to treat invasive fungal infections in immunocompromised children. The metabolism of voriconazole is saturable, which causes a switch from linear to nonlinear elimination. Although several previously published pharmacokinetic (PK) models described the elimination, none of the studies has identified at which dose or concentration voriconazole elimination switches in individuals. Therefore, we aimed to predict the saturation point in hospitalized paediatric patients to prevent common issues of subtherapeutic and supratherapeutic exposure.

Methods: Patient demographics and therapeutic drug monitoring (TDM) data were retrospectively collected from electronic medical records in Westmead Children's Hospital in Sydney between January 2017 and August 2023. A previously published PK model was selected and fitted using nonlinear mixed-effects modelling (NONMEM).

Results: The original model of Friberg *et al*. was selected, but did not describe the PK of our patient population, as minimization was terminated. Hence, we performed model adaptations and tested 44 models with either linear, nonlinear, or mixed linear-nonlinear clearance. None of the nonlinear or mixed linear-nonlinear clearance models resulted in biologically plausible PK parameter estimates. In contrast, a two-compartment model featuring first-order delayed absorption adapted from the original Friberg model resulted in biologically plausible PK parameter estimates. This model featured fixed values for the absorption constant (K_a = 1.19 h^{-1}), absorption delay (A_{lag} = 0.949 h), oral bioavailability ($\log(F_1)$ = 0.373, 95%CI = -0.521-1.267), central distribution volume (V_c = 125 L/70 kg, 95%CI = 63.26-186.74), peripheral distribution volume (V_p = 73.9 L/70 kg, 95%CI = 28.43-119.37), linear clearance (CL = 8.42 L/h/70 kg, 95%CI = 6.23-10.62), intercompartmental clearance (Q = 1.88 L/h/70 kg, 95%CI = -0.354-4.11) with exponential random effects on CL. However, this model both over- and underpredicted voriconazole exposure in our population.

Conclusion: The original Friberg model and derived models were not able to fit our voriconazole data. Thus, the saturation point could not be predicted.

Keywords: *voriconazole, pharmacokinetic model, saturation, dose optimization, paediatrics*