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Performance of Individualized Bayesian Dosage Adjustment for Voriconazole: a simulation study

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Introduction

Voriconazole (VRC) is an anti-fungal agent used in the treatment and prevention of invasive fungal infection. Using both pharmacokinetic (PK) and pharmacodynamic (PD) data, Pascual et al. [1] proposed a therapeutic interval of 1.5-4.5 mg/L for VRC trough concentrations in blood plasma and suggested the administration of an oral dose of 400 mg B.I.D. in adult patients. However, due to a high inter-individual variability in observed plasma concentrations, a single dosing scheme leads to many patients having VRC trough concentrations falling outside the therapeutic interval, making some of them at risk of undergoing an ineffective therapy or developing severe side effects. By adjusting the VRC dosage to individual patient 's needs, Therapeutic Drug Monitoring (TDM) has the potential to significantly increase the chances of a successful therapy while decreasing the risk of adverse events for the patient.

Objective

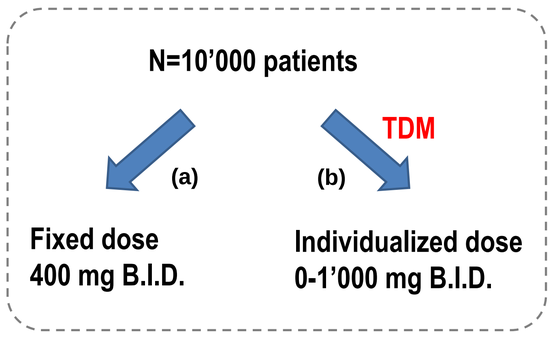
Use Monte-Carlo simulations from the population PK model in [1] to assess the performance of TDM and Individualized Bayesian Dosage Adjustment when administering VRC orally B.I.D. in adult patients with invasive fungal infection.

Method

Simulated trough concentrations for N=10'000 fictive patients with normal hepatic functions were generated using the the population PK model developed in [1]. The simulation design considered the oral administration of VRC B.I.D. with plasma trough concentrations measured every 24 hours. Two situations were simulated:

(a) All patients receive a fixed oral dose of 400 mg VRC B.I.D.

(b) Each patient receives an adjusted VRC dose so that his/her predicted trough concentration (*a posteriori*) at steady-state lies in the center of the therapeutic interval (geometric mean of limits)



In case (b), the optimal dose was selected on a grid ranging from 0 to 1'000 mg, with 50 mg increments.

The proportion of patients with simulated VRC trough concentrations above / within / below the therapeutic interval was calculated under each design.

For a single patient, 95% prediction intervals for trough concentrations at the measurement occasions were calculated both *a priori* (i.e. using the patient's covariate information only) and *a posteriori* (i.e. using both the patient's covariate information and his/her past concentration measurements). *A posteriori* prediction intervals were calculated using the Sampling Importance Resampling (SIR) algorithm [2,3] while treating population parameters in the population PK model in [1] as fixed.

Conclusions

- **TDM of Voriconazole with Individualized Bayesian Dosage Adjustment can significantly increase the proportion of patients with trough concentrations falling in the therapeutic interval compared to a fixed dosing regimen.**
- ***A posteriori* prediction intervals for a single patient represent an effective graphical tool to visualize the probability for future trough concentrations to lie within the therapeutic range and can be easily communicated to the attending physician to assess whether a new concentration measurement is adequate and/or expected for his/her patient under the current or an alternative dosing regimen.**

Results

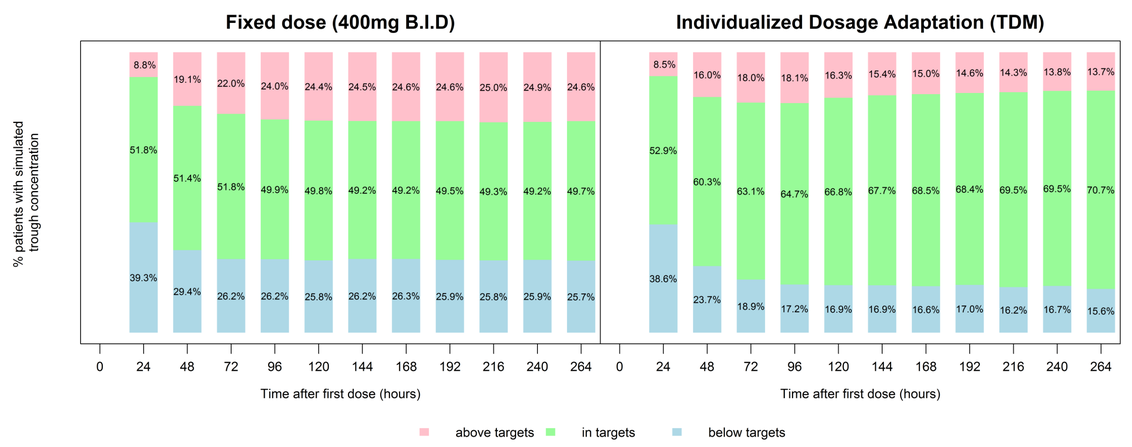


Figure 1: Proportion of patients with trough concentration above / within / below the therapeutic interval proposed in [1] (1.5-4.5 mg/L) under a fixed dosing regimen (400 mg B.I.D.) or using TDM with individualized bayesian dosage adaptation.

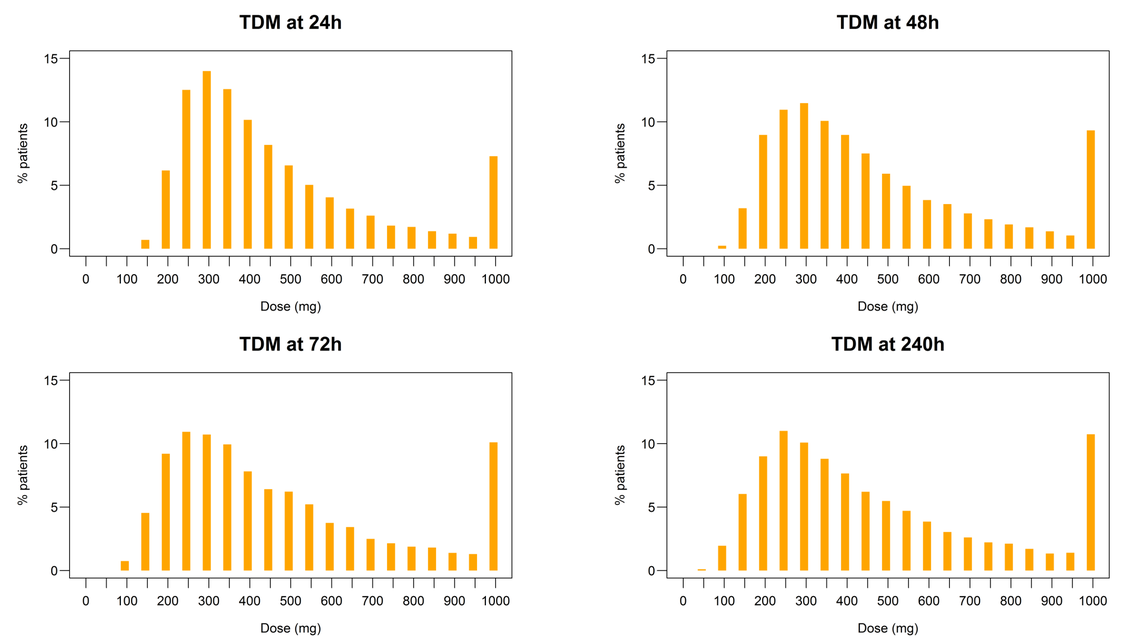


Figure 2: Distribution of adjusted doses at various time points when simulated patients are undergoing TDM.

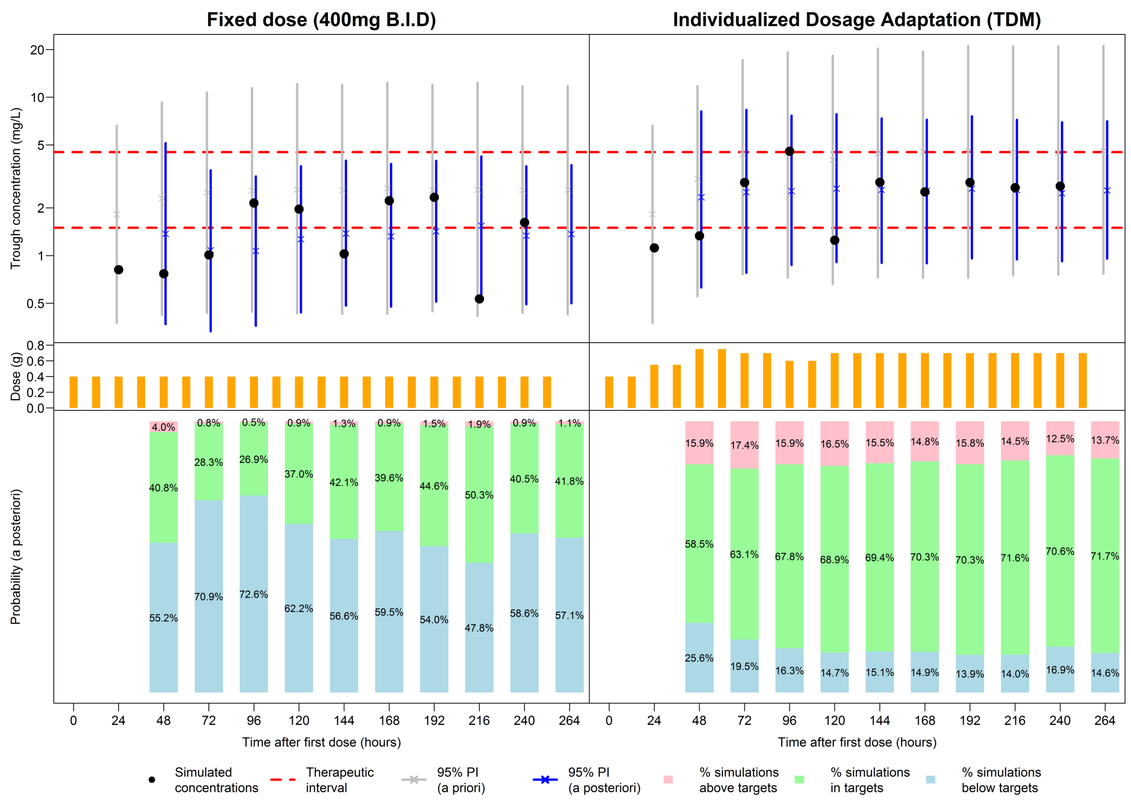


Figure 3: Simulated trough concentrations for a single patient under either a fixed dosing regimen (400 mg B.I.D.) or an individualized dosing regimen using TDM, with *a priori* and *a posteriori* 95% prediction intervals (PI) for trough concentrations, and *a posteriori* probabilities for future trough concentrations to lie above / within / below the therapeutic interval.

References

[1] Pascual A. et al. (2012) Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clinical Infectious Diseases* 55 (3) 381-390

[2] Rubin D.B. (1988) Using the SIR algorithm to simulate posterior distributions. *Bayesian Statistics* 3, 395-402

[3] Smith A.F.M. and Gelfand A.E. (1992) Bayesian statistics without tears: a sampling resampling perspective. *The American Statistician* 46 (2) 84-88