DISCREPANCIES BETWEEN OBSERVED VORICONAZOLE CLEARANCE AND PREDICTED ACCORDING TO CYP2C19 GENETIC POLYMORPHISM. IMPORTANCE OF THERAPEUTIC DRUG MONITORING

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Background and Importance

Voriconazole requires therapeutic drug monitoring (TDM) due to its saturable hepatic metabolism and significant interindividual variability in plasma concentration influenced by genetic polymorphisms, hepatic dysfunction, C-reactive protein (CRP) levels and drug interactions.

Aim and Objectives

To assess whether the voriconazole dosing, adjusted through TDM to reach optimal blood levels, corresponded to that expected according to the patient's CYP2C19 genotype

Materials and Methods

Voriconazole treatments

Comparative analysis: TDM-guided dosing ***vs*** CYP2C19 polymorphism-based dosing
Clearance discordant → ≥30% difference from reference values [1]

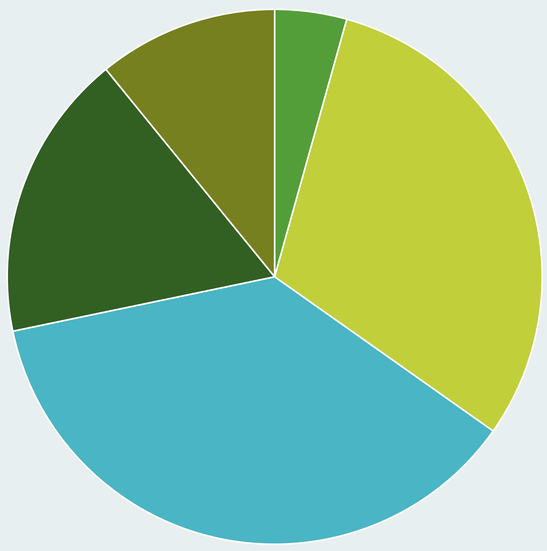
TDM: Avg. 3.5 plasma concentration measurements/patient
Voriconazole Target range: 1-5.5 µg/ml
Dose adjustments: Bayesian modeling (Abbottbase PKS)
Method: Homogeneous enzyme immunoassay

VS

CYP2C19 Method: CRP-based (PHARM-CYP2C19 kit, Generi-Biotech)

Results

Classification metabolizers



Number of patients	46
Age	65.1 (21-93)
Sex	♂ 71.4% ♀ 28.6%
Discordance	**45.7%**
Factors contributing to the discordances	• Drug interactions (2) ➢ Rifampicin ➢ Carbamazepine • CRP levels > 120 mg/l (3)

12 patients showed **slower**-than-expected elimination
- 6 rapid (Cl=1.13 *vs* 4*)
- 5 normal (Cl=0.87 *vs* 3.5*)
- 1 ultra-rapid (Cl=0.92 *vs* 8*)

7 patients showed a **higher**-than-expected clearance
- 4 normal (Cl=5.59 *vs* 3.5*)
- 1 intermediate (Cl=9.15 *vs* 1.5*)
- 2 poor (Cl=2.11 *vs* 0.1*)

* Clearance median (Cl) measured in ml/min/kg

Conclusions and Relevance

TDM is crucial for optimizing plasma concentrations, as many patients had unexpected clearance based on their CYP2C19 genotype, though genotype remains an important covariate in voriconazole TDM.

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[1] Zubiaur, Pablo et al. "Evaluation of Voriconazole CYP2C19 Phenotype-Guided Dose Adjustments by Physiologically Based Pharmacokinetic Modeling." Clinical pharmacokinetics vol. 60,2 (2021): 261-270. doi:10.1007/s40262-020-00941-8

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