

4CPS-024: DEVELOPMENT OF A PHARMACOGENOMIC TOOL FOR OPTIMIZING INTRAVENOUS VORICONAZOLE DOSING BASED ON CYP2C19 POLYMORPHISMS AND DRUG INTERACTIONS

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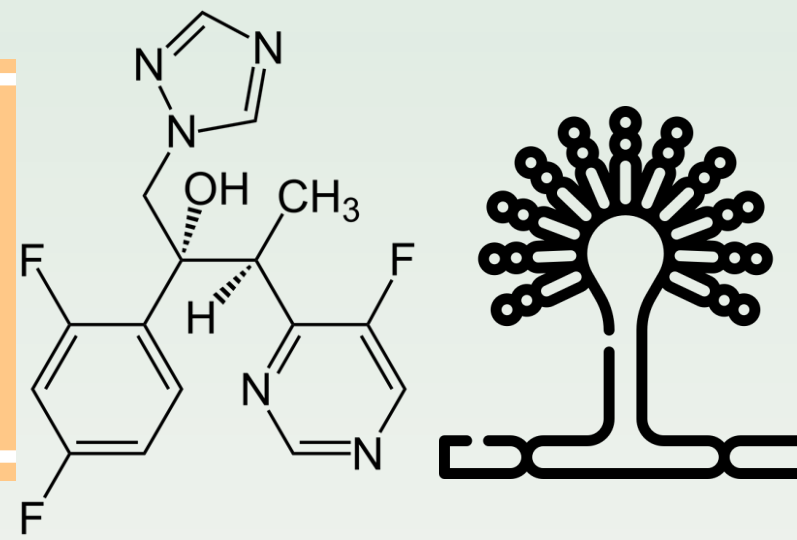
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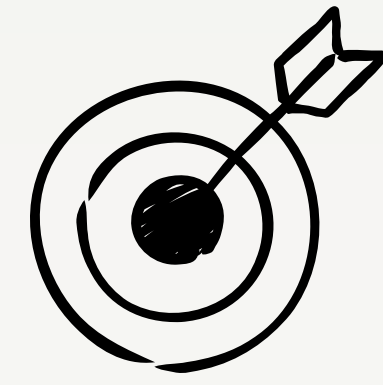


Background and importance



- Voriconazole non-linear pharmacokinetics, narrow therapeutic index and CYP2C19-polymorphism justify therapeutic drug monitoring.
- Intravenous (IV) adult dosage is 6mg/kg/12h followed by 4mg/kg/12h.

Aim and objectives



To develop a **pharmacogenomics-calculator** to optimize IV voriconazole dosing based on **CYP2C19-polymorphism** and **drug interactions**.

Materials and Methods



C++ implementation of a published pharmacokinetic model (Dolton et al.)

Validation in NONMEM

Simulation in R (MRGSOLVE and ggplot2)

Development of a **pharmacogenomics-calculator** with Shiny

Table 1: Pharmacokinetic model covariables

Covariables	Classification	Drugs
Drug-drug interactions	Enzyme inducers (IND)	Rifampicin/phenytoin Dexamethasone
	Enzyme inhibitors (INH)	Low-dose ritonavir
CYP2C19 polymorphism	Metaboliser phenotype	CYP2C19 genotype
	Loss-of-function (LoF)	*1/*2, *1/*3, *2/*17, *2/*2, *2/*3, *3/*3
	Normal-function (NF)	*1/*1

SIMULATIONS

- **Virtual patient** (75kg): treatment target (curative/prophylactic), CYP2C19 polymorphism (LoF/NF) and drug interactions (IND/INH).
- **Efficacy** was assessed via steady-state trough concentrations (C_{min}): **curative (2-5.5mg/L) or prophylactic (1-5.5mg/L) target intervals (TI)**.
- **Rifampicin/phenytoin** simulations included a **dose escalation to 5mg/kg/12h**.

Results



Table 2: TI achievement in twenty concentration-time simulations performed in a virtual patient (75kg).

Dosification (75kg)	Treatment target	Drug-drug interactions	NF (C _{min} , mg/L)	LoF (C _{min} , mg/L)
LD: 6mg/kg iv q12h (450mg/12h)	Curative (TI: 2-5.5mg/L)	No IND/INH	3.04	9.8
		Rifampicin/phenytoin	0.23	1.83
		Rifampicin/phenytoin *dose-escalation	0.32	2.85
		Dexamethasone	1.07	6.46
		Low-dose ritonavir	9.52	13.99
MD: 4mg/kg iv q12h (300mg/12h)	Prophylactic (TI: 1-5.5mg/L)	No IND/INH	3.04	9.8
		Rifampicin/phenytoin	0.23	1.83
		Rifampicin/phenytoin *dose-escalation	0.32	2.85
		Dexamethasone	1.07	6.46
		Low-dose ritonavir	9.52	13.99

LD: loading dose; MD: maintenance dose.

*Dose-escalation: 5mg/kg iv q12h (375mg/12h)

Subtherapeutic; TI in range; Supratherapeutic

Conclusion and relevance



- Standard dosing poses a higher toxicity risk with ritonavir, and in LoF patients without IND/INH or with dexamethasone.
- When co-administered with rifampicin/phenytoin, dose escalation is required.
- A pharmacogenomics-calculator enables individualized IV voriconazole dosing based on CYP2C19-polymorphism and drug interactions.
- As a limitation, the pharmacokinetic model excludes gain-of-function (GoF) metabolisers.