Population Pharmacokinetics and Effect of Voriconazole in Adults Patients for Concentrations Profile Optimization

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Introduction

- Voriconazole (VRC) is a recently commercialized antifungal azole with potent activity against a broad spectrum of medically important fungi.
- It is characterised by a large inter- and intra-patient variability, attributed to genetic polymorphism of *CYP2C19* ad non genetic factors which include age, liver disease, drug-drug interactions
- Increasing evidence have shown a correlation between voriconazole exposure and either failure to therapy and/or toxicity

Dosage individualization based on plasma concentration monitoring (TDM) needs to be confirmed

Aim of the study

- to describe VRC population kinetics in severely ill patients
- to estimate inter and intrapatient variability and the influence of demographic, physiopathological and environmental factors on VRC kinetics
- to derive concentration-effect/toxicity relationships
- to define a dosing regimen achieving appropriate drug exposure in order to improve voriconazole efficacy and safety profiles

Methods

Population:

505 plasma samples from 55 consecutive adult inpatients over a 30-month period receiving VRC treatment

Treatments:

VRC orally (100-400 mg) or iv (body-weight adjusted regimen) twice daily, adjusted according to TDM

Covariates:

sex, body weight, age, co-medications, cholestic hepatitis (severe alkaline phosphatase (A Ph) and/or gammaglutamyltransferase (GGT) increased levels)

Bioanalysis:

VRC blood levels were measured on days 2, 7, and 14 of antifungal therapy and analysed by HPLC

Population PK (NONMEM® program version VI)

- A linear 1-compartment model with first order absorption and elimination on log-transformed data was used
- Inter-patient (IIV) on CL and F and inter-occasion (IOV) variability on F was assigned using exponential random effects
- Covariate analysis: linear relationships between pharmacokinetic parameters and covariate effect
- Derived parameters from the final Bayesian estimates:
  - log-transformed VRC exposure (AUC_{12h})
  - log-transformed peak (C_{max}) & trough (C_{min}) levels

PK-effect relationship

Individual AUC_{12h}, C_{max} and C_{min} and time of exposure were correlated with treatment outcome (relapse) and SNC toxicity using logistic regression models (Stata version 10)

Simulations

VRC concentration-time profile in 1'000 individuals after 200 mg, 300 mg or 400 mg twice daily (iv and oral administration)

These simulations allowed to derived the concentrations under 1 mg/L at trough in more than 80 % of patients with a minimun number of patients exceeding the 5 mg/L limit.

References

- A. Pascual et al.Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes. **Clinical Infectious Diseases 2008; 46:201–11**
- Variability of Voriconazole Plasma Levels Measured by New High-Performance Liquid Chromatography and Bioassay Methods. **AAC 2007; 51:137–143**

Results: PK POP

VRC pharmacokinetic parameter estimates:

	Population mean		Interindividual variability [a]	
Parameter	Estimate	CI_{95} [b]	Estimate (%)	s.e[c] (%)
CL (L/h)	5.2	4.0-6.3	40	50
V (L)	92	63-120	--	
ka (h^{-1})	1.1	0.6-1.6	--	
F	0.63	0.30-0.87	84[g]	68
$\theta_{rifampicin}$ [d]	3.0	2.4-3.6	--	
$\theta_{cholestasis}$ [e]	- 0.52	0.42-0.62	--	
IOV[h]	93	52[c]		62
σ_{prop} (CV %) [f]	59			34

CL, clearance; V, volume of distribution of the central compartment; ka, absorption rate constant; F, bioavailability; IOV interoccasion variability.

a estimates of variability expressed as a coefficient of variation (CV%).

b 95% confidence interval around the mean estimate. For F, the antilog of the 95 % CI derived from the logit function is reported.

c s.e. = standard error of the coefficient of variations, taken as $\sqrt{s.e._{estimate}^2}$ / estimate , expressed as a percentage.

d relative increase in CL in presence of rifampicine coadministration

e relative decrease in CL in case of severe hepatic cholestasis

f residual variability in the plasma concentrations expressed as coefficient of variation CV %).

g estimates of variability on F within the logit function.

h interoccasion variability within the logit function

- A significant inter-dose variability in VRC oral bioavailability was observed
- A decrease in CL by 52 % was observed in patients showing signs of a grade 3 A Ph and/or GGT increased levels
- VRC elimination was markedly increase (300 %) by co-administration with rifampicine
- A modest but non significant inhibition of VRC by the *CYP2C19* inhibitor omeprazole (20%) was observed
- VRC kinetics was linear over the 100-400 mg dosage regimen

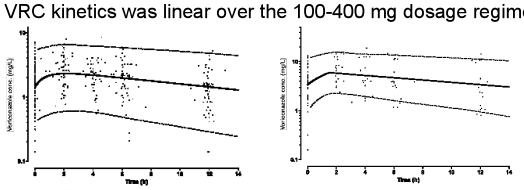
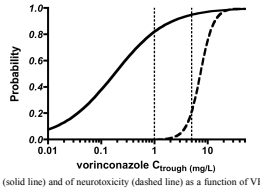


Figure 1: left panel. VRC steady-state plasma concentrations normalized for a 200 mg oral dose (open circles, n=173) and after a 400 mg loading dose (black circles, n=23). Right panel. VRC steady-state plasma concentrations (open circles, n=126) normalized for a 300 mg intravenous dose (1.5 h short infusion). The solid line represents the population prediction an the dashed lines the 90 % prediction interval.

Results: Concentration-Effect Relationships

- VRC AUC_{12h} and C_{min} are significant predictor of antifungal response after oral ($p < 0.03$, OR = 2.5 CI95 1.1-5.7) but not after iv administration of the drug ($p = 0.9$)
- C_{min} or AUC_{12h} and time of exposure revealed a stronger correlation with antifungal response ($p < 0.0001$, OR = 3.1 CI_{95} 1.4-6.6)
- A significant association between AUC_{12h}, C_{min} or C_{max} and neurotoxicity ($p < 0.0001$) was observed, independently of the time of exposure and the route of administration.
- The logistic regression model associates a probability of successful outcome of 82 % at a concentration of 1 mg/L and 93 % at 4 mg/L, the 5 mg/L level being however linked to a 20 % probability of neurotoxicity



Representation of the logistic regression model predicting the probability of therapeutic outcome (solid line) and of neurotoxicity (dashed line) as a function of VRC concentration. The vertical dotted lines indicate the 1 to 5 mg/L therapeutic interval proposed.

Dosage regimen recommendations

- An oral dosage regimen of 300 mg twice daily is better suited than the currently recommended dosage of 200 mg twice daily to achieve drug concentration within the therapeutic range of 1-5 mg/L to optimize efficacy and safety outcomes
- The large variability in VRC absorption and elimination suggests the need of TDM to identify individuals with inappropriate exposure in order to adjust their dosage regimen.