Bedside Sample Time Collection to Improve Model Informed Precision Dosing for Patient Care

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Background

- The aim of model informed precision dosing (MIPD) is to individualize drug doses from pharmacokinetic or pharmacodynamic observation(s) together with a population model
- The clinical utility of MIPD may be influenced by the quantity and timing of observation(s) collected
- Informative observation(s) lead to increased precision in individual parameter estimates while uninformative observation(s) may add limited information to the prior, and negate any potential benefits of MIPD

Aim

- The aim of this analysis is to illustrate how sample times can be optimized for MIPD of the anti-fungal voriconazole

Methods

- A clinically plausible sampling design space was selected that allowed three samples within the first 48 hours of therapy
- A published voriconazole population PK model was available[1] which showed 2-compartment behaviour with mixed linear and non-linear elimination
- A set of sampling time points were identified within the constraints of the design space which maximise the determinant of the maximum a posteriori information matrix (IM_{MAP})
- The IM_{MAP} was defined as

$$IM_{MAP} = J\Sigma^{-1}J^T + \Omega^{-1}$$

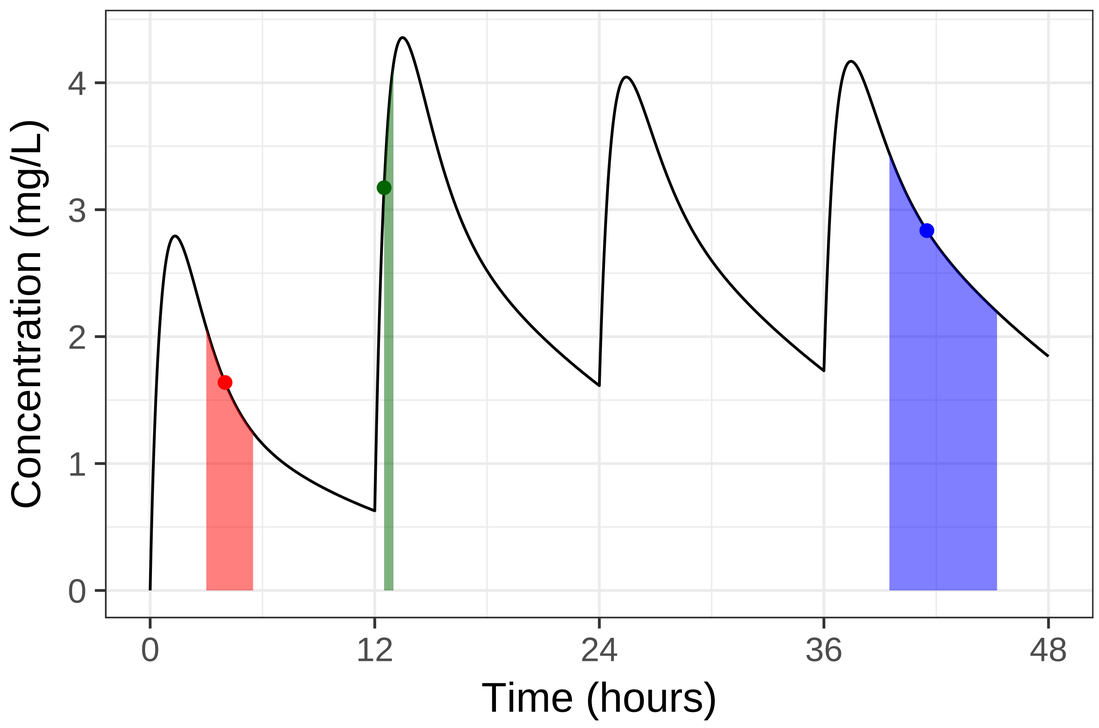
  where J is the Jacobian matrix of dimensions p x n, Σ is the RUV matrix of dimensions n x n, Ω is the prior information matrix of dimensions p x p, p is the number structural parameters in the model, n represents number of optimal time points, and ^{T} denotes the transpose of a matrix
- The variance-covariance matrix was scaled to reduce the prior information for the PK parameters with the largest impact on the target trough concentration (C_{trough})
- The design space was searched using an exchange algorithm to derive robust D-optimal sampling times
- Joint sampling windows were determined using an efficiency criterion of $\geq$0.9
- The performance of the optimal design was assessed by comparing the variance in the estimates with concentrations at the optimal times to the prior information

Results

- The Ω matrix was scaled by the vector of relative importances shown below, with the PK parameters, CL, V_{max} and K_M having the largest impact on C_{trough}

Parameter	Relative Importance
CL	116
V_{max}	290
K_M	58.1
V_c	0.64
V_p	4.70
Q	2.37
KA	1 (Reference)

- The optimal sampling times for voriconazole MIPD were 4 hours, 12.5 hours, and 41.5 hours following the start of Q12H dosing
- The joint sampling windows derived are displayed in the figure below



Solid lines = typical concentration-time profile, dots = optimal sampling times, shaded areas = joint sampling windows

- The reduction in the variance of the parameters using the optimal samples are displayed in the table below
- A significant reduction in variance was observed with the parameters of interest; CL (36.0%), V_{max} (62.3%), and K_M (32.8%)

Parameter	Estimation Variance (%CV)		Reduction in Estimation Variance (%)
	Prior Model	With Optimal Samples	
V_{max}	70	43	62.3
V_c	30	22	46.2
KA	30	23	41.2
CL	45	36	36.0
K_M	100	82	32.8
V_p	30	29	6.6
Q	30	30	0

Conclusions

- Samples collected during the joint sampling windows will likely result in increased precision in parameter estimates and allow valuable dose recommendations through MIPD
- The application of optimal design for MIPD is rarely discussed and should improve the clinical utility of this approach, and ultimately patient outcomes

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References

1. Determination of a suitable voriconazole pharmacokinetic model for personalised dosing. J Pharmacokinet Pharmacodyn. 2016 Apr;43(2):165-77

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