EV0009

# Comparative evaluation of the predictive performance of three different structural population pharmacokinetic models to predict future voriconazole concentrations

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## ABSTRACT

**Objectives:** Therapeutic drug monitoring (TDM) of voriconazole in clinical practice has been strongly advocated in recent years to improve the safety and efficacy profile of this agent. Bayesian methods for voriconazole TDM have been studied before but there are no reports comparing the accuracy and precision of predictions of published models. Furthermore, the comparative accuracy of linear, mixed linear and non-linear, or fully nonlinear models may be of interest. The goal of this study was to compare the performance of these three methods coupled with Bayesian feedback for predicting voriconazole concentrations.

**Methods:** Voriconazole concentrations from an independent dataset of hematopoietic stem cell recipient patients were used in this analysis. Voriconazole was administered by intermittent IV infusion. The models were coded into Individually Designed Optimum Dosing Strategies (ID-ODS™) online and used as the Bayesian prior in a sequential design. Observed levels were predicted where for each concentration the data available to that point were entered and used to estimate a prediction. The mean prediction error (ME) and mean squared prediction error (MSE) and their 95% confidence intervals (95%CI) were calculated to measure absolute bias and precision, while delta ME (Δ ME) and delta MSE (Δ MSE) and their 95% CI to measure relative bias and precision, respectively.

**Results:** 317 voriconazole levels were analyzed. MEs (95%CI) ranged from 0.02 (-0.08, 0.13), 0.29 (0.20, 0.38) to 0.3 (0.20 to 0.39) while the MSEs (95%CI) from 0.91 (0.60, 1.21), 0.73 (0.54, 0.93), to 0.81 (0.58 to 1.05) for the linear, mixed, and non-linear models, respectively, indicating a non-significant difference in bias for the linear method. When compared relative to the linear method, both the mixed and non-linear approaches showed higher Δ MEs of 0.26 (0.19, 0.33) to 0.27 (0.17, 0.37) and non-significantly lower Δ MSEs of -0.17 (-0.39, 0.05) and -0.09 (-0.39, 0.20), respectively.

**Conclusion:** Simulations with the linear model were found to be more accurate and similarly precise at predicting voriconazole concentrations versus the mixed or non-linear method evaluated here. Further analyses are needed to determine predictive performance following orally administered voriconazole and the performance of linear models in patients who display significant saturation of voriconazole elimination.

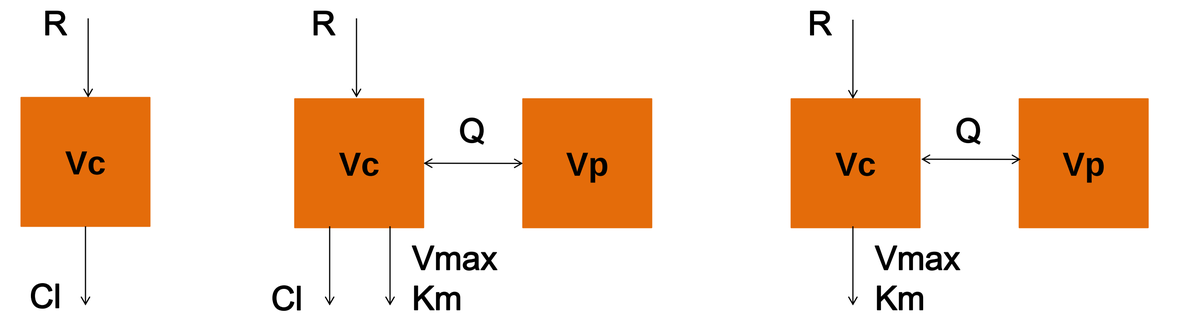
## INTRODUCTION AND OBJECTIVES

- A variety of structural models have been used for voriconazole (VOR) concentration predictions given the complex pharmacokinetics of this agent.[1,2,3]
- For serum concentration data, the Bayesian approach appears to improve predictive performance, but no comparison exists on the predictive performance of the different structural models evaluated in a sequential design.[4]
- The goal of this study was to compare the accuracy and precision of the linear, mixed linear and non-linear, or fully non-linear models with Bayesian feedback in a sequential design for predicting VOR concentrations.

## METHODS

- VOR concentrations from an independent dataset of hematopoietic stem cell recipient patients were used in this analysis (n=10).
- The ID – ODS™ application was used to predict VOR concentrations using a one and two compartment linear, mixed linear and non-linear, and fully non-linear intravenous infusion models. [5]
- The FME package was utilized to carry out the Bayesian analysis via the Markov Chain Monte Carlo technique using the Metropolis – Hastings algorithm.[6]
- Analysis of prediction errors was based on calculated mean (ME) and delta mean prediction errors (ΔME) and mean squared (MSE) and delta mean squared prediction errors (ΔMSE) using the R® software.[6]

## METHODS




*R* represents the infusion rate of VOR, *Cl* (in liters per hour) is the clearance, *Vc* is the volume of the central compartment (in liters), *Vp* is the volume of the peripheral compartment (in liters), $V_{max}$ is the maximum rate of clearance by the Michaelis-Menten clearance mechanism (in milligrams per hour), $K_m$ is the concentration of VOR where the clearance by the Michaelis-Menten mechanism is half maximal (in milligrams per liter), *Q* is the intercompartmental clearance (in liters per hour).

**Figure 1. Structural mathematical models evaluated in this analysis from left to right: Pascual et al., Ping et al., and Dolton et al.**

## RESULTS

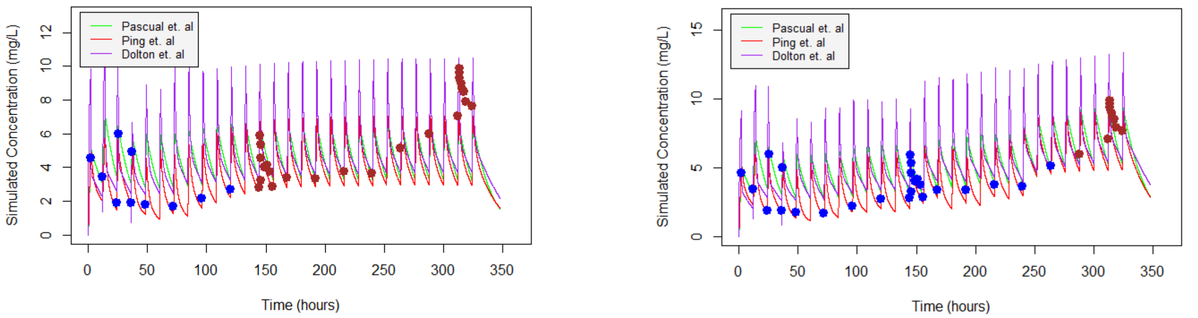



**Figure 2. Observed versus predicted concentration – time profiles for Patient #3 (blue dots represent concentrations used to establish Bayesian models to predict future concentrations colored in burgundy)**

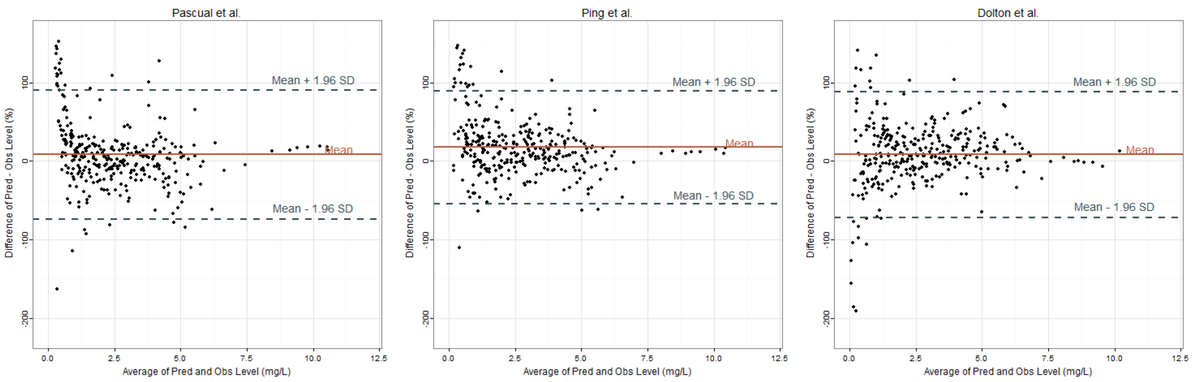



**Figure 3. Percent difference Bland – Altman plot of observed versus predicted concentrations**

## RESULTS

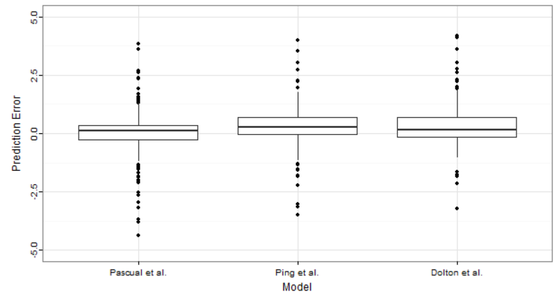



**Figure 4. Box plot of calculated prediction errors versus observed concentrations**

| Model | BIAS AND PRECISION VERSUS OBSERVED | | | |
|---|---|---|---|---|
| | Mean Prediction Error (mg/L) | | Mean Square Prediction Error (mg/L) | |
| | Mean | 95% CI | Mean | 95% CI |
| Pascual | 0.02 | -0.08 to 0.13 | 0.91 | 0.60 to 1.21 |
| Ping | 0.29 | 0.20 to 0.38 | 0.73 | 0.54 to 0.93 |
| Dolton | 0.30 | 0.20 to 0.39 | 0.81 | 0.58 to 1.05 |

**Table 1. Summary statistics of absolute performance indicators**

| Model | BIAS AND PRECISION VERSUS PASCUAL MODEL | | | |
|---|---|---|---|---|
| | Δ Mean Prediction Error (mg/L) | | Δ Mean Square Prediction Error (mg/L) | |
| | Mean | 95% CI | Mean | 95% CI |
| Ping | 0.26 | 0.19 to 0.33 | -0.17 | -0.39 to 0.05 |
| Dolton | 0.27 | 0.17 to 0.37 | -0.09 | -0.39 to 0.20 |

**Table 2. Summary statistics of relative performance indicators**

## CONCLUSION

- Using absolute and relative performance, simulations with Bayesian feedback using linear, mixed linear and non-linear, or fully non-linear models were found to be similarly precise, while the linear method resulted in better accuracy of predicted VOR concentrations in this group of patients.
- Based on the results presented here, all of the structural models evaluated seem to be reasonable for use in a clinical TDM program focusing on the optimal dosing of VOR
- Further evaluation of the performance of these models in patients who may exhibit significant saturation pharmacokinetics of this agent is warranted in the future.

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