The Impact of Model Selection for Personalised Dosing

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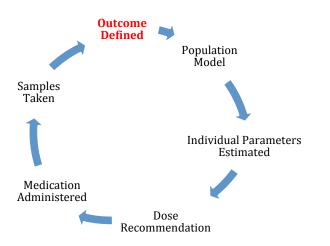
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Introduction	Methods	Results	Conclusions
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Model Based Personalised Dosing (MBPD)



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Barriers to MBPD in the Clinical Setting

1 Limited evidence of improved clinical outcomes

- 2 Limited intuitive integrated software packages
- 3 Limited understanding from clinicians

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Barriers to MBPD in the Clinical Setting

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Barriers to MBPD in the Clinical Setting

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Model Selection

How close is good enough?

"Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful"

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Voriconazole

- Broad-spectrum triazole antifungal
 - Non-linear elimination
 - Large BSV
 - TDM is advocated
- Nine published POP PK models
- The models differs significantly
 - Clearance mechanisms
 - Covariates included



Methods

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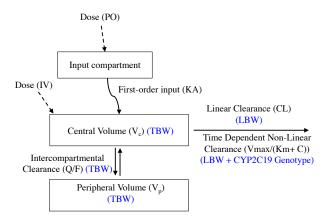
- 1 Develop misspecified population PK models
- 2 Calculate dose recommendations from the misspecified models
- 3 Predict the likely exposure under these dose recommendations
- Extrapolate the probability of clinical outcomes (success / toxicity)

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Methods: Overview

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Reference Model Published Model (Hybrid) - JPKPD 2016:43(2)



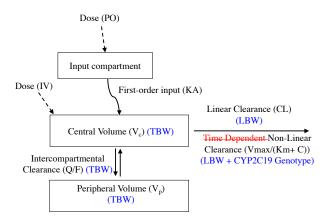
 $\mathsf{TBW} = \mathsf{total} \ \mathsf{body} \ \mathsf{weight}, \ \mathsf{LBW} = \mathsf{lean} \ \mathsf{body} \ \mathsf{weight}, \ \mathsf{Blue} = \mathsf{covariate} \ \mathsf{effect}$

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Misspecified 1 No Time Dependent Elminiation



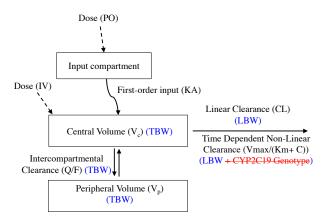
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Misspecified 2 No CYP2C19 genotype as a covariate



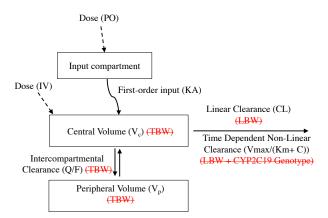
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Misspecified 3 No covariates



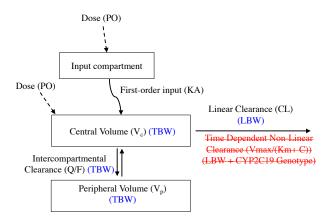
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Misspecified 4 Linear Elimination Only



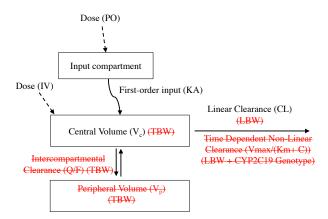
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Misspecified 5 Linear Elimination, 1 CMT, No Covariates



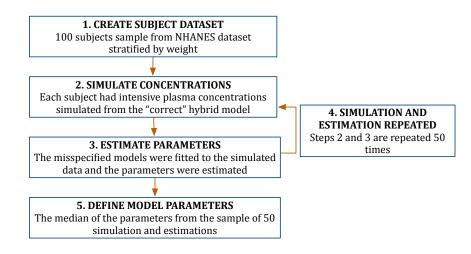
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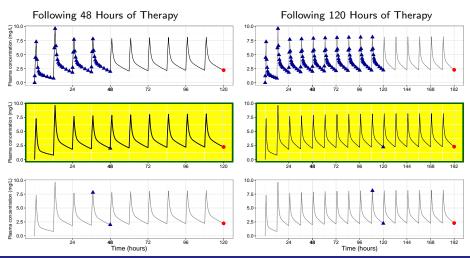
Methods: Misspecified Model Parameters Estimates



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Methods: Scenarios Considered



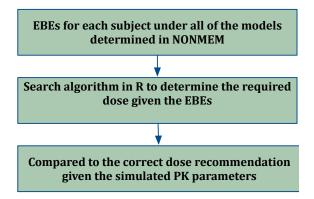
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Methods: Dose Adjustment Required

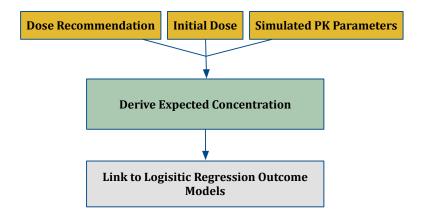


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Methods: Plasma Concentrations Achieved & Clinical Outcomes



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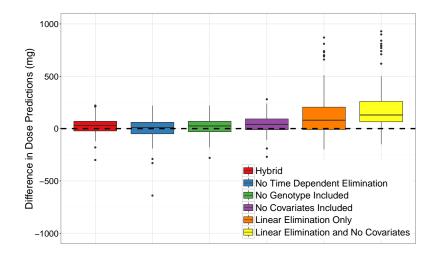
Results

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Dose Recommendations: Following 120 Hours of Therapy

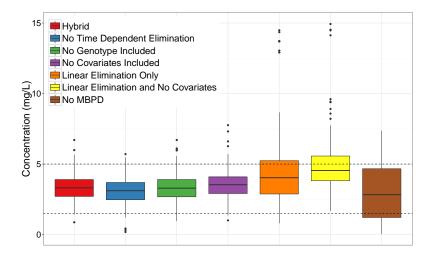


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Placma Concentrations Proc	licted		

Plasma Concentrations: Following 120 Hours of Therapy

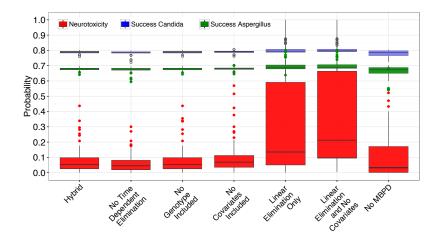


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Destablished Clinical Order			

Clinical Outcomes: Following 120 Hours of Therapy



Conclusions

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Conclusions: What is Important

Structurally miss-specified clearance

- Large, clinically relevant impact on dosage decisions and plasma concentrations achieved
- Removing non-linear clearance from the models resulted in poor performance

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Conclusions: What is Important

Structurally miss-specified clearance
MAJORARTICLE
Challenging Recommended Oral and Intravenous Voriconazole Doses for Improved Efficacy and Safety: Population Pharmacokinetics–Based Analysis of Adult Patients With Invasive Fungal Infections

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Conclusions: What is Not Important

CYP2C19 Genotype and Other Covariates

- An individuals genotype is often not known prior to dosing
- The utility of knowing their genotype once plasma concentrations become available is unclear
- Removing genotype from the model was of little clinical importance

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This research has several limitations

- Simulation study
- Assume the correct model
- IV therapy only
- Accepted in AAPS Journal

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Acknowledgments

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