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INTRODUCTION:

Model Based Personalised Dosing (MBPD) or Bayesian Dose Forecasting is a sophisticated form of personalised medicine that relies upon software to determine the optimal dose of a medication for an individual. The concept is not however new, and was first described by Sheiner in 1969 as a method for monitoring anticoagulant therapy.(1) MBPD can be divided into two arms, parametric and non-parametric, with this paper specifically focusing on parametric MBPD.

In order to undertake MBPD, a population pharmacokinetic (PK) or pharmacodynamic (PD) model is required that adequately describes the dose-exposure or dose-response relationship. The model serves as prior information, i.e. a Bayesian prior, which can be used to determine initial drug doses that target a specific exposure (e.g. AUC), by accounting for subject specific covariates that describe some of the variability in PK (e.g. weight, renal function). After patient specific PK or PD results become available, the true utility of MBPD becomes apparent. By using the individual PK or PD observations together with covariate information, the parameters and subsequent dose are determined for the individual patient, rather than the average patient. As the number of individual observations increases, the model based predictions become more personalised, and less population based. When using a MBPD approach, the user or software developer must select an appropriate population model to be used clinically. This is not however a trivial process, as several models are likely to be published in the literature for the same drug. As development of population models is subjective in nature(2), and relies upon study design that

effects how informative the data is i.e. number and type of subjects, number and timing of observations, models presented in the literature will often differ significantly with regard to structure and the covariate effects included. Choosing one population PK model over another for MBPD could potentially result in large, clinically significant differences in dose recommendations. The aim of this paper is to therefore assess the impact on dose recommendations of implementing structurally miss-specified population PK models in MBPD using voriconazole as a motivating example.

MATERIALS AND METHODS:

Currently there are nine different population PK models published in the literature for voriconazole(3-11). The models were each developed in different populations i.e. paediatric or adult subjects, under different conditions, and naturally differ in the number of compartments estimated. More importantly these models differ in clearance mechanisms due to doses administered and timing of the PK observations. In our previous work, we developed a hybrid population PK model for voriconazole that incorporated all the available evidence from the population PK models published in the literature.(12) Briefly, the hybrid model is a two-compartment disposition model, with mixed linear and time-dependent non-linear clearance that includes CYP2C19 genotype and body weight as covariates on clearance, and body weight as a covariate on central and peripheral volume of distribution.

Reduced Models:

Here, we determine the impact of using miss-specified population PK models on dose predictions, by comparing dose predictions between the hybrid model, which was considered to be the correct model, and the following five reduced models (Table 1), herein described using the following notation:

- 1) **Non-Time** dependent **L**inear and **Non-L**inear **E**limination with **2-Compartment** disposition (**NTL-NLE-2C**);
- 2) **Non-Genotype** dependent **L**inear and **Non-L**inear **E**limination with **2-Compartment** disposition (**NGL-NLE-2C**);
- 3) **Non-Covariate** included with **L**inear and **Non-L**inear **E**limination and **2-Compartment** disposition (**NCL-NLE-2C**);
- 4) **L**inear **E**limination with **2-Compartment** disposition (**LE-2C**);
- 5) **No Covariates** included with **L**inear **E**limination and **1-Compartment** disposition (**NC-LE-1C**).

Parameters for the reduced models were developed using the stochastic simulation and estimation (SSE) functionality in PsN,(13) where the hybrid model was used for simulation, and the parameters were re-estimated under the alternate models described above.

The dataset used for the SSEs consisted of one hundred subjects randomly selected from the National Health and Nutrition Examination Survey (NHANES) dataset (1999-2010) stratified by weight, with ten subjects per 10 kg range between 30-130 kg selected. As the overall the prevalence of CYP2C19 poor metabolisers (PM) is 1-20% depending on ethnicity,(14, 15) CYP2C19 genotype

was randomly assigned to each subject with 10% allocated as PM. Lean body weight (LBW) for adults was determined using the Janmahasatian equation,(16) with an adjustment made for paediatric subjects.(17) Each subject was randomly allocated a loading dose of 4, 6 or 8 mg/kg every twelve hours (q12h) for two doses, followed by a maintenance dose of 2, 4 or 6 mg/kg q12h. A saturated PK sampling design was used with plasma concentrations simulated every 15 minutes until 4 hour post-dose and then every two hours until 12 hours post dose, after one, two, three, five and eight doses. Trough plasma concentrations were simulated for the remaining doses up to dose sixteen. Fifty SSEs for each of the reduced models were performed, with the parameters for each of the reduced models defined as the median estimates from the SSE.

Dose Predictions:

The same 100 virtual patients used previously were assigned a dosage regimen consistent with the product label.(18) Adult subjects received 6mg/kg q12h for two doses, and then 4mg/kg q12h for another 8 doses. Paediatric subjects (<12 and 12-15 years old weighing < 50kg), received 9mg/kg q12h for two doses followed by 6mg/kg q12h for another 8 doses. Plasma concentrations were simulated from the hybrid model with intensive sampling every 15 minutes until 4 hour post-dose and then every two hours until 12 hours post dose out to 120 hours using NONMEM. (19) The dose predictions for the virtual subjects under the hybrid and reduced models were determined for both a saturated design where all samples were available for the MBPD predictions, and a clinical design where limited samples were available for the MPBD predictions. The sampling schedules of the saturated and clinical designs are displayed in Figure 1.

Saturated design:

Initially the first 48 hours of intensive sampling was used to obtain empirical Bayes' estimates (EBEs) of the individuals PK parameters under each of the reduced models and the "correct" hybrid model. Next, a search algorithm was developed in R⁽²⁰⁾ to identify the optimal dose adjustment required (rounded to the closest 10 mg i.e. 1 mL of solution) to obtain the target plasma concentration (3 mg/L) at 120 hours (i.e. three days time). The deSolve package in R, which uses the Livermore Solver for Ordinary Differential Equations (LSODA), was employed to solve the differential equations. The same methodology was followed using 120 hours of intensive sampling to estimate the individual's optimal dose to obtain the target plasma concentration at 192 hours (three days time).

Clinical design:

Dose- estimation under a clinical design followed the same methods as the saturated design, however; only one (trough) or two (peak and trough) plasma concentrations were available for the MBPD recommendations. Firstly, a single trough level (Clinical 1) at 48 hours was used to estimate the individual's optimal dose to obtain the target plasma concentration at 120 hours. Secondly, this was repeated under a two-level approach (Clinical 2) using a peak plasma level at 37 hours combined with a trough at 48 hours. Thirdly, a single trough level at 120 hours was available to predict the optimal dose to achieve the target plasma concentration at 192 hours. Finally, this was repeated by combining a peak level at 109 hours with a trough level at 120 hours.

Clinical limits applied:

Using the previously defined dose recommendations an arbitrary limit of twice the maximum licensed dose (i.e. up to a double of the dose) was applied to all dose recommendations.

The dosage recommendations from the hybrid and reduced models in the saturated and clinical designs were compared directly to the “correct” dose required to obtain a plasma concentration closest to 3 mg/L given the simulated PK parameters.

Predicted plasma concentrations:

The plasma concentrations that are predicted under the dose recommendation from the prior section were simulated in R. The predicted plasma concentrations achieved using the reduced models for MBPD were compared directly to the plasma concentration achieved from using both the “correct” hybrid model for MBPD, and without personalised dose adjustments. The percentage of subjects within the therapeutic range (1.5 - 5) and the median and absolute maximum concentration for subjects outside the range were reported.

Clinical outcomes:

Logistic regression models linking exposure to clinical response(21) and neurotoxicity(6) were applied to the predicted plasma concentrations previously described to assess the probability of clinical outcomes under MBPD. The following equations were used:

$$\ln\left(\frac{P_s}{1-P_s}\right) = 0.596 + 0.128 \cdot \ln\left(\frac{CONC}{MIC}\right)$$

$$\ln\left(\frac{P_r}{1-P_r}\right) = -7.22 + 3.66 \cdot \ln(CONC)$$

where P_s is the probability of success, P_r is the probability of toxicity, $CONC$ is the trough plasma concentration, and MIC is the minimum inhibitory concentration for the pathogen. As the trough concentration to minimum inhibitory concentration (MIC) ratio was used as the exposure metric in the clinical response model, the probability was assessed for both infections with *Candida albicans* (MIC 0.012 µg/ml) and *Aspergillus fumigatus* (MIC 1 µg/ml) with the respective MIC derived from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. (22)

RESULTS:

Parameter estimates:

The parameter estimates for the hybrid and reduced population PK models are displayed in Table 1. Removal of the time-dependent maximum metabolic rate (V_{max}) (NTL-NLE-2C), resulted in a low estimate of the Michaelis constant (K_m) with large between subject variability (BSV), indicating non-linear clearance at low concentrations with large variability.

Dose recommendations:

The difference in dose recommendations under the hybrid and reduced models are displayed in Table 2 and Figure 2. As expected, the “correct” hybrid model performed well, with dose recommendations closely aligned with the optimal

doses. Removing the time-dependent clearance (NTL-NLE-2C) resulted in lower dose recommendations than required (50 mg & 40 mg at 48 and 120 hours respectively), under a saturated design. Under the clinical designs the median dose recommendations were closer to the required doses at both 48 and 120 hours. Removing CYP2C19 genotype and CYP2C19 genotype and body weight (NGL-NLE-2C and NCL-NLE-2C) resulted in similar dosage recommendations to the required doses under both the saturated and clinical designs at both 48 and 120 hours. The models with linear clearance only (LE-2C & NC-LE-2C) performed poorly, recommending several large doses. This was especially observed in subjects whom initially had a low voriconazole concentration.

Predicted plasma concentrations:

The plasma concentrations that would have been obtained by following the dose recommendations from the hybrid and reduced models, given the known PK parameters, are displayed in Figure 3. The percentage of subjects within the therapeutic range as well as the median and absolute maximum concentration outside the therapeutic range for subjects above or below the therapeutic range is available in supplemental 1 & 2. When non-linear clearance was included in the models, close to 90% of the plasma concentrations were within the therapeutic range under all the simulated scenarios. The impact of removing covariates (genotype +/- body weight) under the clinical scenarios had minimal impact on the plasma concentrations achieved and percentage of subjects within the therapeutic range compared with the hybrid model. When non-linear clearance was not included in the model, MBPD performed poorly with both the saturated and clinical designs and resulted in dangerously high concentrations.

The clinical limits of twice the licensed dose were applied on 11% to 49% of the subjects depending upon the model (supplemental 1 & 2). The plasma concentrations that would have been obtained by following the dose recommendations from the hybrid and reduced models, given the known PK parameters and the clinical limits, are available in Supplemental3. The application of clinical limits improved the performance of the models with linear clearance by increasing the percentage of patients within the therapeutic range by an average of 29%. This did not impact the utility of the models with non-linear clearance as they retained < 90% of subjects within the therapeutic range.

Clinical outcomes:

The probabilities of both clinical response and neurotoxicity when a single trough sample was available to guide dosing decisions is displayed in Figure 4. The probability of clinical response was similar across all the models investigated, and marginally lower when MBPD was not used (no dose adjustments). The probability of neurotoxicity was lowest when the model contained non-linear clearance. 75% of the subjects had a probability of less than 10% of neurotoxicity. The probability of the adverse effect greatly increased when a model with linear clearance was used, a reflection of the larger dose recommendations. When no MBPD was used, the overall probability of neurotoxicity was greater than when a model with non-linear clearance was used.

DISCUSSION:

As famously quoted by George Box, “Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful”. (23) This is a highly applicable question in the area of MBPD, as medicines often have several population PK models published in the literature and the dose-recommendations achieved by the implementation of different population PK models can be significantly different. An important question to consider when selecting a population PK model for MBPD is “how miss-specified does the population PK models chosen have to be, to clinically impact on dosage decisions and ultimately patient outcomes?” This paper explores this question using voriconazole as a motivating example.

Both saturated and clinical designs were investigated at 48 hours and 120 hours of sampling in the 100 virtual subjects. When limited samples were available, the time of the sampling had a potentially large impact on the ability to estimate PK parameters (i.e. peak samples contain little information on clearance or elimination rate). The saturated design is aimed at answering a methodological question, that is, to estimate PK parameters with miss-specified models, taking the design and time of the samples from the study out of the equation. It is impractical however in a clinical setting to have access to intensive sampling to inform dose decisions. In fact, one the major theoretical benefits of MBPD is the ability to have prior beliefs in the form of the population PK model that are updated with the individuals PK or PD result. Rather than use optimal design to identify the optimal time for sampling a practical approach was taken to obtain trough or trough and peak levels.

Structurally miss-specified clearance:

Overall it was clear that structurally miss-specified clearance has a large, clinically relevant impact on dosage decisions, plasma concentrations achieved, and likelihood of neurotoxicity. Removing non-linear clearance from the models resulted in poor performance with several extreme dose, recommendations of up to 62,000 mg for the models with linear clearance only. Only 66% and 25% of subjects were within the therapeutic range at 120 hours with saturated sampling for 48 hours for the respective models. This was improved with 120 hours of saturated sampling available, with 69% and 64% subjects having a plasma concentration between 1.5-5mg/L at 192 hours, and similar improvements were seen under both clinical designs. This is extremely relevant for voriconazole as several population models are published in the literature with linear clearance(3, 6, 8, 10, 11), although it is largely accepted from the rest of the literature base that voriconazole exhibits saturated non-linear clearance via CYP2C19. (24, 25) It is most likely these models could not identify a non-linear clearance component due to study design alone. If these models were implemented in MBPD, dangerously high doses would be recommended and more harm than benefit may result compared to not using MBPD.

A time-dependent $V_{\max}$ was included in the hybrid model due to auto-inhibition of metabolism reported in the literature(9), and the impact of removing this structural parameter was explored with the NT-NLK-2CT reduced model.

Removing this parameter resulted in an under prediction of the required dose by an average of 50 mg and 40 mg after both 48 and 120 hours of intensive sampling, respectively. However, under the clinical designs, where limited

samples were available, the dosage recommendations were closer to the required dose. The variations are of little clinical importance for dosage recommendation as the percentage of subjects within the therapeutic range and the probability of the clinical outcomes assessed was comparable to the correct hybrid model.

Missing Covariates:

The importance of genotype in MBPD was explored by removing genotype from the hybrid model. It has been well demonstrated in the literature; that on average a subject's CYP2C19 genotype has a large impact on its ability to clear voriconazole and the subsequent exposure achieved.(14, 26, 27) As such, CYP2C19 genotype was included as a covariate in the hybrid model with a reduction in $V_{\max}$ for poor metabolisers of 41%. It is undeniable that genotype will play a role in initial dose recommendations; however, an individual's genotype is often not known prior to dosing, and the utility of knowing their genotype once plasma concentrations become available is unclear. Removing genotype from the model (NG-LNLE-2C) resulted in modest increases in the median recommended dose of between 20 – 30 mg under the clinical scenarios. As displayed in Figures 3 and 4, this is of little clinical importance as the model performed as well as the hybrid model in terms of percentage of subjects within the therapeutic range, the median and maximum concentrations achieved for the subjects outside of range, and the probability of clinical response and neurotoxicity. The results indicate that once plasma concentrations become available, the benefit of genotype in MBPD is of little to no benefit.

Additionally, removing all covariates (body weight and genotype) from the model had very little impact on plasma concentrations achieved. An identical 85% of subjects were within the therapeutic range under both clinical designs for the reduced and hybrid models using samples to 48 hours. Similar results were seen with sampling out to 120 hours. There was a small difference in the median and maximum concentrations above or below the therapeutic range for the 10-15% of subjects outside the therapeutic range.

Clinical limits:

Clinical limits are often applied to dose recommendations from MBPD as a safety mechanism. It can provide protection from unusual patients, incorrect data entry, and miss-specified population PK models. Applying an arbitrary limit of twice the licensed dosage was applied to all dose recommendations. For the models with linear clearance, both the percentage of subjects within the therapeutic range and the maximum and median value missing the therapeutic range improved as well as the probability of neurotoxicity. For the models with non-linear clearance, the percentage of subjects within the therapeutic range remained consistent. When the time-dependent clearance was removed from the model, the benefits of the clinical limits were seen in the magnitude of missing the therapeutic range for the minority of subjects outside the target.

Clinical Design:

Overall the clinical design with one sample only performed well when non-linear clearance was included in the models, with very little benefit evident from adding a peak sample.

CONCLUSION:

To our knowledge, this is the first paper to investigate the impact of model-misspecification on MBPD. The removal of important structural model components can have a large impact on the clinical utility of MBPD, and for voriconazole, the exclusion of non-linear clearance resulted in poor dose predictions, performing models, whilst removing time-dependent clearance was of less importance. Removing patient covariates (CYP2C19 genotype and body weight) from the models had no clinically significant impact on the utility of MBPD.

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Table I Hybrid and Reduced Model Parameters

Parameter	Hybrid	NT-NLE-2C	NG-LNLE-2C	NC-LNLE-2C	LE-2C	NC-LE-1C
Fixed Effects						
K _m (mg/L)	1.92	0.19	1.77	2.63		
V _{max,1} (mg/hr)	110	11.2	100	134		
V _{max,inh}	0.82		0.82	0.82		
T ₅₀ (hr)	2.41		2.4	2.48		
CL (L/hr)	3.6	4.18	3.5	3.21	7.54	9.85
Exp on LBW for CL & V _{max}	0.31	0.35	0.31		0.27	
% V _{max,1} in PM	0.59	0.61				
V _c (L)	59	60.6	55.6	60.6	66.1	120
V _p (L)	79	144	75.8	74.9	164	
Q (L/hr)	27	30.4	25.9	24.5	25.9	
Exp on TBW for V _c	1	0.99	0.98		0.96	
Exp on TBW for V _p	1	0.82	1		1.03	
Exp on TBW for Q	1	0.98	1		1.23	
BSV (% CV)						
K _m	100	250	87	116		
V _{max}	71	61	73	77		
CL	45	73	46	53	76	65
V _c	55	55	54	70	55	59
V _p	55	72	56	65	123	
RUV (%CV)						
Proportional	32	37	32	33	38	48

Parameters for the reduced models were obtained using stochastic simulation and estimation in NONMEM. NT-NLE-2C refers to the reduced model with time-dependence clearance removed. NG-LNLE-2C refers the reduced model with genotype removed. NC-LNLE-2C refers the reduced model with all covariates removed. LE-2C refers the reduced model with non-linear clearance removed. NC-LE-1C refers to the reduced model with non-linear clearance, genotypes and the peripheral compartment removed. K_m = Michaelis constant, V_{max} = maximum metabolic rate, V_{max,1} = V_{max} at 1 hour, V_{max,inh} = maximum proportion of inhibition of V_{max}, T₅₀ = time to 50% of inhibition of V_{max}, CL = clearance, Exp on LBW = exponent on lean body weight, PM = poor metabolisers, V_c = central volume of distribution, V_p = peripheral volume of distribution, Q = intercompartmental clearance, TBW = total body weight, BSV = between-subject variability, RUV = residual unexplained variability. V_{max} parameterised as $V_{max} = V_{max,1} \cdot (T-1) / [(T-1) + (T_{50}-1)]$ in

Hybrid, NG-LNLE-2C, and NC-LNLE-2C. BSV and RUV represented as %CV which is equal to $100 \cdot \sqrt{\text{Variance}}$

Table IIa Difference in Dose Recommendations made after 48 hours of therapy

Model	Median (mg)	IQR (mg)	Range (mg)
Hybrid	-10	-30 - 20	-120 - 160
Hybrid C1	30	-30 - 72.5	-370 - 210
Hybrid C2	25	-30 - 72.5	-340 - 210
NT-NLE-2C	-50	-100 - 0	-340 - 1090
NT-NLE-2C C1	20	-40 - 70	-620 - 280
NT-NLE-2C C2	20	-30 - 80	-600 - 270
NG-LNLE-2C	-5	-30 - 20	-110 - 230
NG-LNLE-2C C1	20	-30 - 72.5	-340 - 220
NG-LNLE-2C C2	20	-30 - 72.5	-310 - 230
NC-LNLE-2C	0	-30 - 50	-120 - 460
NC-LNLE-2C C1	40	-2.5 - 100	-340 - 240
NC-LNLE-2C C2	30	-10 - 100	-310 - 240
LE-2C	-10	-80 - 257.5	-340 - 43550
LE-2C C1	155	20 - 455	-150 - 46040
LE-2C C2	150	20 - 425	-160 - 46040
NC-LE-1C	340	175 - 902.5	10 - 62920
NC-LE-1C C1	310	130 - 602.5	-100 - 48510
NC-LE-1C C2	320	120 - 582.5	-130 - 48620

IQR equals inter-quartile range. C1 refers to Clinical 1, which represent when a single concentration at 48 hours of therapy is used to inform dose recommendations. C2 refers to Clinical 2, which represents when two concentrations at 37 and 48 hours are used to inform dose recommendations. NT-NLE-2C refers to the reduced model with time-dependence clearance removed. NG-LNLE-2C refers the reduced model with genotype removed. NC-LNLE-2C refers the reduced model with all covariates removed. LE-2C refers the reduced model with non-linear clearance removed. NC-LE-1C refers to the reduced model with non-linear clearance, genotypes and the peripheral compartment removed.

Table IIb Difference in Dose Recommendations made after 120 hours of therapy

Model	Median (mg)	IQR (mg)	Range (mg)
Hybrid	-10	-30 - 10	-160 - 180
Hybrid C1	30	-22.5 - 70	-300 - 220
Hybrid C2	25	-32.5 - 80	-290 - 220
NT-NLE-2C	-40	-80 - -10	-300 - 710
NT-NLE-2C C1	10	-50 - -60	-640 - 220
NT-NLE-2C C2	10	-60 - -60	-630 - 180
NG-LNLE-2C	-10	-30 - 10	-150 - 200
NG-LNLE-2C C1	25	-30 - 70	-280 - 220
NG-LNLE-2C C2	30	-32.5 - 90	-260 - 220
NC-LNLE-2C	0	-30 - 20	-170 - 250
NC-LNLE-2C C1	40	-10 - 92.5	-270 - 280
NC-LNLE-2C C2	40	-10 - 100	-260 - 270
LE-2C	-10	-60 - 152.5	-200 - 18970
LE-2C C1	125	20 - 347.5	-200 - 32040
LE-2C C2	90	-10 - 315	-370 - 31950
NC-LE-1C	120	60 - 505	-60 - 42640
NC-LE-1C C1	180	70 - 390	-150 - 34090
NC-LE-1C C2	160	80 - 387.5	-140 - 33550

IQR equals inter-quartile range. C1 refers to Clinical 1, which represent when a single concentration at 120 hours of therapy is used to inform dose recommendations. C2 refers to Clinical 2, which represents when two concentrations at 109 and 120 hours are used to inform dose recommendations. NT-NLE-2C refers to the reduced model with time-dependence clearance removed. NG-LNLE-2C refers the reduced model with genotype removed. NC-LNLE-2C refers the reduced model with all covariates removed. LE-2C refers the reduced model with non-linear clearance removed. NC-LE-1C refers to the reduced model with non-linear clearance, genotypes and the peripheral compartment removed.