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A mathematical model for warfarin reversal using vitamin K

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Presentation type Oral

Presenters Anna Cao

Introduction: Vitamin K is indicated for warfarin reversal when active bleeding is present or when there is a high risk of bleeding (INR > 5). However, choosing an appropriate dose of vitamin K is challenging due to our limited understanding of the dose-response relationship and the interactions between warfarin and the vitamin K cycle. For instance, an unexpectedly prolonged resistance to warfarin has been reported with the use of vitamin K for warfarin reversal. The aim of this study was to develop a mechanistic mathematical model to describe the interactions between warfarin and vitamin K cycle, and to use the model to explore the underpinning enzyme kinetics that are consistent with pharmacodynamic outcomes observed during warfarin initiation, warfarin overdose, and warfarin reversal with vitamin K.

Methods: The model structure was derived based on individual mechanistic components identified from the literature. The system was described by a set of 18 ordinary differential equations, with 11 reactions/fluxes and 43 parameters. Simulations from the model were conducted in MATLAB Version R2017a (The MathWorks, Inc., Natick, Massachusetts, United States). Initial estimates of the parameters were set to values derived from the published literature or arbitrary values if such values were unavailable. Parameter values were then calibrated heuristically to achieve reported steady-state amounts for five moieties of interest: vitamin K epoxide, vitamin K quinone, vitamin K hydroquinone, coagulation proteins, and the international normalised ratio for three scenarios: (1) physiological condition, (2) warfarin maintenance therapy, and (3) warfarin reversal with vitamin K.

Results: The model developed performed acceptably in simulating the five states of interest for all the three different scenarios. In the initial stage, the model, which specified that vitamin K reduction can only occur via the vitamin K epoxide reductase (VKOR), was not able to replicate the effect of vitamin K on reversing warfarin overdose. However, when an alternative (putative non-VKOR pathway) for vitamin K reduction was introduced, the rapid reversal effect of vitamin K on warfarin was able to be captured

adequately. This finding is significant because it highlights the importance of the alternative pathway in reversing warfarin overdose which has not been well explored in previous studies.

Discussion: This model serves as a starting point to improve our current understanding of warfarin and the vitamin K system. Further work is required to refine the model. The model may be applied to explore various clinical scenarios and to determine suitable dose and frequency to administer vitamin K for effective warfarin reversal.

Quantifying the Dose-Response of Unfractionated Heparin Using a System Pharmacology Model of Coagulation

January 6, 2019

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Presentation type Oral

Presenters Abdallah Derbalah

Introduction: Unfractionated heparin (UFH) is commonly used in the treatment and prevention of a variety of thromboembolic disorders. Its short duration of action and reversibility of its effect with the use of protamine sulphate make it the agent of choice in acute settings such as cardiac surgery. However, optimal dosing of UFH remains challenging partly due to the lack of quantification of its pharmacokinetic (PK) properties and the lack of a universal and direct pharmacodynamic (PD) biomarker. In addition, interpretation of the PD response is distorted by the inherent variability of the haemostatic system upon which UFH acts.

Aim: To explore the use of a systems pharmacology model of coagulation to simulate the dose-response relationship of UFH.

Methods: The coagulation model by Wajima [1] was modified to allow for dose titration used to simulate the time course of anti-Xa and activated partial thromboplastin time (aPTT) activity of UFH following IV infusion. Anti-Xa response was calculated through polynomial regression of the Xa clotting time (XaCT) predicted by the coagulation model [2]. Data were available on 31 paediatric patients who received UFH for thromboprophylaxis during extracorporeal membrane oxygenation procedure. UFH infusion rate was titrated to maintain a target anti-Xa level of 0.4-0.6 IU/mL. The simulated anti-Xa and aPTT responses were overlaid with observed data. No modelling was performed.

Results: Observations-overlaid prediction plots showed reasonable model agreement for model predictions and the individual data for anti-Xa activity. In general there was reasonable agreement between the model predictions and aPTT observations in some patients. In contrast, in other patients the model predictions were significantly different from the observations (generally underpredicting the observations by 2-3 fold at usual

clinical infusion rates). It is possible that this might be due to the supersensivity of some children to UFH.

Conclusion: Simulations from the model showed that it can adequately describe the time course of anti-Xa activity during UFH infusion. Further refinement of the model is required to be able to describe the aPTT response, particularly in some children. The model can then be used as a basis for quantifying the dose-response relationship of UFH and will be extended further to account for its time varying pharmacokinetics.

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The Influence of Genotype on Warfarin Dose Predictions

January 7, 2019

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Presentation type Oral

Presenters Guangda Ma

Background & Aims: Warfarin is the most commonly prescribed oral anticoagulant worldwide, however, a narrow therapeutic range poses a barrier to safe and effective therapy. Common methods to predict warfarin dose requirements are biased at the extremes. When evaluated by simulation, Bayesian dose forecasting using a theory-based warfarin PKPD model achieves unbiased and precise dose predictions across the full range of clinical doses (1). Despite the association between genotype and warfarin dose requirements, current evidence is not sufficiently robust to support genotype-guided warfarin therapy. The theory-based PKPD model for warfarin accounts for the influence of genotype on warfarin PKPD (2).
Aim 1: evaluate the performance of the model against an external, clinically derived dataset (3).

Aim 2: evaluate the influence of genotype knowledge on the performance of warfarin dose predictions.

Methods: NONMEM 7.4.1 was used to simulate 1000 virtual patients by sampling sex, age, weight, CYP2C9, VKORC1 and CYP4F2 covariates before warfarin doses were individualised using a genotype-known or genotype-missing model. The model predicted maintenance dose was used to individualise doses on days 1-3, before INR measurements on days 3, 7, 10, 14, 21, 28, 35, 42, 49, and 56 were used to individualise daily doses to achieve an INR of 2.5.
The performance of genotype-known and genotype-missing dose individualisation were compared using measures of bias (mean prediction error, ME), imprecision (root mean square error, RMSE) and time within the therapeutic range (INR 2.0-3.0) during days 4-14 (TTR4-14) and days 15-28 (TTR15-28).

An external evaluation of the model was performed by using the model to predict the maintenance dose for 138 patients (data provided by Dr Dan Wright (New Zealand) and Dr Alison Thompson (Scotland)). The model predicted maintenance dose was compared with the clinically observed target dose.

Results: Measures of predictive performance were similar for the genotype guided (ME: -0.016 mg/day, 95% CI: -0.186, 0.155 mg/day; RMSE: 0.45 mg/day) and genotype missing simulations (ME: 0.0004 mg/day; 95% CI: -0.169, 0.17 mg/day; RMSE: 0.512 mg/day) over the simulated dose range of 0.77-27 mg/day.
Genotype-guided dosing (TTR4-14: 29%; TTR15-28: 69%) was not clinically different from genotype-missing dosing (TTR4-14: 30%; TTR15-28: 69%).

External evaluation of warfarin was unbiased (ME: 0.12, 2.5th percentile: -0.91 mg/day, 97.5th percentile: 1.45 mg/day) and precise (RMSE: 0.58 mg/day) over the actual dose range of 0.75-11 mg/day.

Conclusion: Unbiased and precise warfarin dose predictions were achieved using the theory-based PKPD model in simulation, and external evaluation. The addition of genotype knowledge does not improve Bayesian dose forecasting using the theory-based PKPD model for warfarin. The minimal benefit for TTR4-14 when genotype information is used is consistent with the magnitude of effects observed in clinical trials but without the bias attributable to different dosing methods.

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A review of current infusion regimens of propofol in neonates and infants

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Presentation type Oral
Presenters James D Morse

There are no validated propofol infusion regimens in neonates and infants. Existing pharmacokinetic pharmacodynamic (PKPD) models do not include data from babies under the age of 1 year (1) making dosing in this population empirical, largely based on recommendations from Steur *et al* (2).

Steur and colleagues recommend a bolus dose between 3-5 $mg \cdot kg^{-1}$ followed by infusion rates unique for age bands (0-3 months, 3-6 months, 6-9 months, 9-12 months and 1-3 years) and these recommendations were obtained by adapting the adult dosage scheme to neonates and infants. The number of propofol boluses and the time from administration to awakening were used as criteria to adjust the dosage scheme, rather than any pharmacokinetic knowledge (2). The recommended bolus dose of propofol is high for this group; known to have immature clearance pathways and smaller distribution volumes, and the resulting concentrations achieved with these doses are unknown.

A PKPD model for propofol target controlled infusions (the Eleveld model) was developed using pooled data from 1033 subjects with ages ranging from 27 weeks post menstrual age (PMA) to 88 years, and included a maturation model to account for changes in clearance with age (3).

This model was used to simulate expected plasma concentrations based on dosing regimens proposed by Steur *et al* in 10 children aged 37 weeks PMA – 2 years. Patient demographics (age, height, weight and normal fat mass) were obtained from an existing dataset (4). Simulations were performed in NONMEM (NONMEM 7.4.1, Icon Development Solutions, USA) with 1000 replications and 95% confidence intervals constructed.

Simulated concentrations are interpreted in the context of a target propofol concentration of 3 $\mu g \cdot ml^{-1}$; associated with an adequate depth of anaesthesia (5). Proposed changes to dosing regimens are given based on the Eleveld model. This is a work in progress.

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A Population Pharmacokinetic Model of Phenobarbitone in Neonates to Determine Oral Bioavailability and Facilitate Individualised Dosing

January 15, 2019

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Presentation type Oral

Presenters Angela Williams

Background: Phenobarbitone is the most commonly used first-line drug for the treatment of neonatal seizures. A number of previous studies, with small subject numbers, have identified covariates that may influence the pharmacokinetics of phenobarbitone but results have been inconsistent. In particular, oral bioavailability is relatively poorly described and doses are commonly reported as being the same for both intravenous and oral administration. However 2 recent studies have reported oral bioavailability as 49% and 59% respectively [1, 2]. A model based on a larger data set may assist in identifying covariates that may impact dosing in these patients.

Methods: A population pharmacokinetic model was built based on routine therapeutic drug monitoring data from 112 infants treated at the Royal Brisbane and Women's Hospital Neonatal Intensive Care Unit. Population modelling was performed using NONMEM 7.3 and PsN 4.7. R studio and the R packages Xpose and VPC were used for data exploration and visualisation. One and two compartment models were tested. Body weight with allometric scaling on Clearance (CL) and Volume of Distribution (V) were included *a priori* in the structural model. Covariates tested included age (post-menstrual, gestational and post-natal), Apgar scores, concomitant treatment with phenytoin, presence of infection and method of nutrition.

Results: A one-compartment model provided an adequate fit to the data. Typical clearance increased with patient post-natal age (PNA) and was best modelled using the equation CL = 5.1 *$WT^{0.75}$* $(PNA/6.25)^{0.43}$(mL/h) were weight is in kg, PNA in days and 6.25 is the median post-natal age. Volume of distribution (V) was best modelled using the equation V = 797 * $WT^{1.0}$(mL). Oral bioavailability (F) was and 85%. Between-subject variability was 25%, 30% and 21% respectively for CL, V and F. Internal model

validation was performed by generating visual predictive check (VPC) and normalised prediction distribution error (npde) plots, and running a non-parametric bootstrap.

Conclusion: This study describes with largest population pharmacokinetic model of phenobarbitone developed to date with estimates of CL and V in line with previously published models. However, the estimate of F is somewhat higher than previously reported but still lower than the assumed F of 100% implied in most recommended dosing regimens. Once externally validated it is intended that this model form the base for the analysis of a larger data set including the covariates of Hypoxic-Ischaemic Encephalopathy and Therapeutic Hypothermia.

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A Population Pharmacokinetic Study of Caffeine Citrate in Chinese Premature Neonates

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Presentation type Oral

Presenters Xiaoyan YANG, Nick HOLFORD

Objective: Apnea of prematurity (AOP) is defined as an attack of apnea for at least 20 seconds, with bradycardia and cyanosis. It is a common phenomenon in the neonatal intensive care unit (NICU). Caffeine citrate, one of the methylxanthines, is used to suppress or to prevent AOP attack. This study aimed to develop a population pharmacokinetic (popPK) model for caffeine after administration to preterm neonates.

Methods: Preterm neonates, who were treated with caffeine citrate, in the NICU of West China Second University Hospital, Sichuan University during Jan, 2015 and Jun, 2017 were enrolled in this study. Serum concentration samples were obtained at 30 min, 4 h, and 12 h after the loading dose, as well as at 30 min before the first and second maintenance dose. Trough concentration samples were obtained every 7 days until caffeine citrate was stopped. All the samples were measured by high-performance liquid chromatography (HPLC). The dosing regimen of caffeine citrate, combination medications, demographic features (such as gestational age (GA), birth weight (BW), delivery pattern, and sex), and laboratory tests of liver and renal function were documented. Renal function (RF) was calculated from the ratio of predicted creatinine clearance (Schwartz1992) to predicted glomerular filtration rate (Rhodin, Anderson et al 2009). A one-compartment model with zero-order input (intravenous), or first-order input (oral), and first order elimination was used to describe the time course of caffeine concentration. Both a maturation effect and a size effect were used to account for changes in post-menstrual age (PMA week) and total body weight (TBW kg). An adult clearance (CL) of caffeine (6.55L/h/70kg) was assumed with renal CL of 1.55% of total clearance (Birkett and Miners 1991). The size effect on clearance and volume of

distribution was described with an allometric model: FSIZECL = (TBW/70)^(3/4) and FSIZEV = (TBW/70)^(1/1). The maturation of caffeine renal CL was assumed to be the same as glomerular filtration rate (Rhodin, Anderson et al 2009): FMATCLR=1/(1+(PMA/47.7)^(-3.4)). The maturation of non-renal CL was expressed as: FMATCLNR=1/(1+(PMA/TM50CL)^(-HILLCL)) where TM50CL is the PMA when CL is 50% of the size standardized adult value and HILLCL is an empirical exponent. The popPK model was developed using NONMEM 7.41. Visual predictive checks (VPC) was performed for model evaluation.

Results: Concentration data (1,004 samples) were obtained from 222 (120 male) preterm neonates, with an average GA of 29.7±1.8 weeks and an average BW of 1.28±0.29 kg. Among all the maintenance doses, 32.49% (1,796/5,528) were administrated orally. The non-renal CL maturation was described by HILLCL = 1.56 while TM50CL was fixed to 300 weeks. Meanwhile, the delivery pattern was found to have effects on total CL (FMATBIRTH = 0.857 while the baby was delivered by caesarean). Thus, the model for total clearance was: CL (L/h) = 6.55 *(0.9885* FMATCLNR + 0.0115*FMATCLR*RF)*FSIZECL*0.857. The model for volume of distribution was: V (L) = 79.7*FSIZEV. For CL the between subject variability (BSV) was9.62% and for V it was 17.1%. The between occasion variability (BOV) for CL was very small (<5%).

Conclusion: As expected the clearance of caffeine in neonates was lower than adults based on size alone because of immature elimination processes. The wide variability in concentrations with a fixed dose regimen and a small BOV for CL suggest measurement of caffeine concentration would be helpful in individualizing doses to reach a safe and effective target concentration (Holford and Buclin 2012).

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A Population Pharmacodynamic Study of Apnea of Prematurity and the Effect of Caffeine Citrate in Chinese Premature Neonates

January 6, 2019

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Presentation type Oral

Presenters Nick Holford

Objective: Apnea of prematurity (AOP) is defined as an attack of apnea for at least 20 seconds, with bradycardia and cyanosis. It is a common phenomenon in the neonatal intensive care unit (NICU). Caffeine is used to suppress or to prevent AOP attacks. Based on a population pharmacokinetic (PK) model for caffeine the effect of caffeine on the hazard of AOP attacks was described.

Methods: The design of the study and the PK analysis have been described separately (Yang, Holford et al. 2019). The baseline hazard was described by a Gompertz distribution. The effect of caffeine was modelled using a sigmoid Emax model directly on the hazard of an AOP attack. Evaluated covariates included various methods of spontaneous breathing ventilation support (LFNC, HFNC, CPAP, BIPAP, BNCPAP) or mechanical ventilation (CMV, HOV). The hazard was set to 0 during mechanical ventilation. The pharmacodynamic (PD) and hazard model was developed using NONMEM 7.41. Visual predictive checks (VPC) was performed for model evaluation.

Results:

The bootstrap hazard and pharmacodynamic parameter estimates are shown in Table 1.

Table 1 Parameters of AOP hazard and pharmacodynamics of caffeine

Parameter	Description	Units	Bootstrap average
L_LZ	Baseline hazard	1/h	0.00496
B_GOM	Gompertz hazard	.	-0.00167
CAF_EMAX	Emax for caffeine effect on hazard	1/h	0.492
CAF_C50	C50 for caffeine effect on hazard	mg/L	1.80
CAF_HILL	Hill exponent for effect on hazard	.	2.64
GGC50	C50 with A2A receptor GG genotype	mg/L	1.57

Conclusion: Caffeine suppresses AOP attacks by about 50%. The C50 suggests that a target concentration of 5 mg/L would achieve close to maximum achievable benefit.

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Reference:

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Modelling of delivery kinetics of gentamicin administered through umbilical long lines

January 15, 2019

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Presentation type Oral

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Introduction: Gentamicin is commonly used in the NICU setting and is often administered via long lines, such as umbilical venous catheters, which increases variability in the rate of administration. This variability is not taken into account when considering drug delivery in neonates and recommendations are extrapolated from adult data. We aimed to model drug delivery parameters and use this model to simulate intravenous gentamicin administered via an umbilical venous catheter.

Methods: Data was modelled from infusion simulations of gentamicin delivery using umbilical venous catheters with a background flow rate of 0.5ml/h (carried out by Anita Lala in 2016). Different combinations of dose (2mg, 5mg) were given by bolus injection over 3-5 minutes, followed by a normal saline flush (1ml, 2ml). The amount of gentamicin at the end of the line was measured at 5 minute intervals for an hour via high pressure liquid chromatography.
Phoenix Certara (version 8.1) was used to model the data previously described. An extravascular model with the clearance removed was used to predict the parameters absorption constant (Ka), time lag (Tlag), and “bioavailability” (F). F was used to enable an estimate of the variability in dose administered. Doses used in the model were the actual doses measured in the study rather than the prescribed dose. Different error models were used to ascertain which best described the data.

Results: An extravascular one compartment model with first order absorption and additive error best described the data. The estimates for this model for a dose of 2mg and a 1ml flush were Ka 0.34L/min, Tlag 1.28min, F 0.97, and stdev of 0.14. The -2LL was -41.8, the epsshrinkage was 0.08, and nshrinkage for ka was 0.9999, Tlag 0.25, and nF 0.03. For 2mg with 2ml flush the estimates were Ka 0.86L/min (95% CI 0.76 – 0.95L/min), Tlag 3.01min (95% CI 1.95 – 4.06min), F 0.87 (95% CI 0.79 – 0.95), and stdev of 0.01 (95% CI 0.006 – 0.011). The condition number was 46.41, the-2LL was -381.75, the epsshrinkage was 0.08, and nshrinkage for ka was 0.9999, Tlag 0.01, and nF 0.001. For 5mg with 1ml flush the estimates were Ka 0.48L/min (95% CI 0.41 –

0.54L/min), Tlag 3.13min (95% CI 1.86 – 4.39min), F 1.03 (95% CI 0.90 – 1.17), and stdev of 0.12 (95% CI 0.08 – 0.16). The condition number was 48.48, the-2LL was -36.24, the epsshrinkage was 0.08, and nshrinkage for ka was 0.9999, Tlag 0.07, and nF 0.0001. For 5mg with 2ml flush the estimates were Ka 0.83L/min (95% CI 0.30 – 1.36L/min), Tlag 3.29 min (95% CI 1.40– 5.19 min), F 1.09 (95% CI 0.96 – 1.21), and stdev of 0.02 (95% CI 0.01 – 0.02). The condition number was 63.92, the-2LL was -218.07, the epsshrinkage was 0.09, and nshrinkage for ka was 0.54, Tlag 0.14, and nF 0.09.

Conclusion: This is the first known modelling of gentamicin delivery kinetics. Therefore, there are no previous studies to compare the estimates obtained to. The studies all had high nshrinkage for Ka, therefore the individual estimates of ka may be unreliable. Further studies with a higher number of replicates would provide more favourable data for estimating Ka.

References:

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Pharmacometric modelling of deuterium exposure in breastfeeding mother-infant pairs for the determination of exclusive breastfeeding practice

January 6, 2019

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Presentation type Oral

Presenters Zheng Liu

Background: The World Health Organization (WHO) recommends exclusive breastfeeding (EBF) for the first 6 months after birth. A stable isotope deuterium dose-to-mother (DTM) technique can be used to determine whether an infant is EBF by estimating quantitatively the intake of breastmilk and non-breastmilk water intake. This method has several advantages as it is non-invasive, simple to perform, robust, and accurate. However, a validated cut-off value of non-breastmilk water intake to distinguish EBF from non-EBF is not available. Also DTM technique is not an ideal field tool for measuring EBF in population-based surveys as it involves 7 days of post-dose saliva sample collections from mother and infant over a 14-day study period. Shortening of the sampling protocol has been proposed but whether it resembles the original protocol remains unknown.

Aims: The 1st aim was to determine a cut-off value of non-breastmilk water intake to distinguish EBF from non-EBF based on analysis of data arising from DTM saliva samples from mother-infant pairs. The 2nd aim was to design a streamlined DTM technique protocol which is more field friendly, i.e. less number of post-dose saliva samples.

Methods: Data were available from 9 countries including 790 mother-infant pairs. The data was split into, (1) model building data set (565 pairs, including 113 EBF-controlled pairs as calibration data); (2) evaluation data set (225 pairs). The model analysis applied a nonlinear hierarchical model in a fully Bayesian framework using a Markov chain Monte Carlo (MCMC) approach implemented in Stan. A four-stage method used: (i) determination of EBF criterion using the calibration data, (ii) assignment of subjects in

the model building data set to EBF or non-EBF categories, (iii) optimising a field friendly study, (iv) evaluation of the optimised design involving the evaluation data set.

Results: Two linked 1-compartment models (mother and infant) with combined error model, and addition of mother's body weight on mother's volume of distribution and infant's body weight on infant's water clearance rate provided an adequate description of the data. One-hundred and thirteen EBF infants were included in the calibration data and using the 90thpercentile of the distribution of the population non-milk water intake, we estimated a cut-off value of 86.6 g/d, with a lower limit 95% CI of approximately 56 g/d [1]. Two post-dose windows (days 7-9 and 13-14) yielded optimal categorisation (>95% sensitivity and specificity) in the model building dataset. This design was validated in the evaluation data set with similar performance.

Discussion: A less time and resource intensive DTM deuterium two-day post-dose sampling design together with the determined cut-off value were found to be capable of separating EBF from non-EBF infants. The design has been used in the field study in Indonesia with more flexibility. The next step is to promote the whole method developed in this study to future field studies.

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Twenty Years of PAGANZ

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Presentation type Oral

Presenters Nick Holford

The PAGANZ 2019 meeting in Auckland celebrates the twentieth PAGANZ meeting held in Australasia. The original speakers at PAGANZ in 1999 who are also present at PAGANZ 2019 reflects the beneficial effect of pharmacometrics on longevity and friendship.

Pharmacometrics is the boom growth field in clinical pharmacology. It has other names which serve local purposes but at its essence it describes the quantitative aspects of disease and pharmacology with the goal of understanding and improving human health.

The history of pharmacometrics in Australasia and the evolution of PAGANZ is documented on the PAGANZ website https://www.paganz.org/history/.
PAGANZ is strongly linked with the international community outside of Australasia through ISoP. Members of PAGANZ have served on the ISoP Board and have had a major impact in moving ISoP from its North American origins to recognize the international scope of this evolving science. PAGANZ hosted the second World Conference on Pharmacometrics in 2016 which showcased the talents and enthusiasm of the people who belong to PAGANZ.

PKPD Explorations Using Paracetamol; 20 years on

January 6, 2019

Authors Brian Anderson

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Presentation type Oral

Presenters Brian Anderson

Paracetamol (acetaminophen) has served as a useful substrate for population modelling and factors determining dose. This modelling has improved not only PKPD understanding of the drug, but has also been useful to explore models that characterize size (e.g., allometry), clearance maturation, the impact of birth on clearance, the role of fat mass, concentration-response relationships, delayed effects, target concentration strategies, toxicity, and pharmacodynamic interactions with other drugs. Lessons have also included the politics of data sharing and factors influencing translation of PKPD knowledge into clinical practice.

Early studies were designed to determine serum concentration after administration of suppositories. However, data were then required to further explore pharmacokinetics [1, 2] of other formulations in different age groups [3-7] and clearance metabolic pathways involved.[8] The use of allometric theory [9-11] allowed standardization for size, rationalization of dosing [12] and exploration of clearance maturation.[13] Rich neonatal data permitted exploration of clearance changes at birth.[14] A review of toxicity and its relationship to absorption and clearance in children aged less than 5 years changed treatment recommendations in those presenting with overdose to emergency departments worldwide.[15]

Target concentration concepts using effect compartment modelling were explored in both children [16-19] and neonates [20]. Appraisal of CSF [21, 22] as the effect compartment was reviewed. These studies resulted in rationalization of dose. However dose has been tempered by fears of hepatotoxicity rather than PKPD considerations. The role of fat for determination of dose [23, 24] has also been explored and paracetamol clearance has been investigated using normal fat mass.[25, 26]

Paracetamol is commonly used in conjunction with NSAIDs. PD Interaction models [27] were used to explore both diclofenac [28] and ibuprofen [29, 30] interactions. These studies introduced concepts of the hazard of dropping out, placebo effects and disease progression.

Many studies were only possible because data were generously shared by colleagues in other countries. However, data retain usefulness for investigators long after an original publication and the politics of data sharing have become a major sticking point for current investigations.[31] The study of paracetamol has been more a journey around PKPD modelling than characterization of the clinical pharmacology of a common analgesic.

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Combining PK and PD data; a 20 year perspective

January 10, 2019

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Presentation type Oral

Presenters Janet R Wade

Twenty years ago there were already many publications about population PK/PD analyses, but no research had been done on the best way to combine PK and PD data. A fundamental assumption of PK/PD analyses was that the PK response drives the PD response. Analysing PK and PD simultaneously was considered to be the gold standard, avoiding that potential PK model miss-specification would inflate PD parameter standard error estimates (SEs), but could be computationally difficult. Sequential PK/PD analysis was computationally simpler but estimation error in the PK is ignored and so PD parameter SEs may be underestimated. A body of simulation work was presented looking at 4 different methods to combine PK and PD data.

1. Simultaneous PK/PD analysis.
2. Fit PK data. Fix individual PK parameters. Fit PD data.
3. Fit PK data. Fix population PK parameters. Fit PD data.
4. Fit PK data. Fix population PK parameters (but retain the PK data in the analysis data file). Fit PD data.

The simulation results of 20 years ago found that methods 1 and 4 performed equally well, and method 2 performed least well.

Moving forward 20 years the fundamental assumption that PK response drives the PD response hasn't changed; or has it….? Two examples will be presented where there is a three-way interaction between the disease/host, PK and PD, and which renders the question of how to best combine PK and PD data still a relevant discussion even today.

From the First to the NextDose: My journey through 20 years of PAGANZ

January 7, 2019

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Presentation type Oral

Presenters Sam Holford

Our overarching aim has been to bring better dosing methods to the ward, meaning we aim not only to make pharmacometric model-based calculations useable by clinicians, but to actually get them to use it. We want doses to be determined by the best possible method, meaning real patients receiving doses that were determined (at least in part), by the most robust and accurate calculation method possible – not just the easiest to understand or most popular protocol.

The project started with FirstDose – an antibiotic dose calculator for paediatric patients. The software went through several iterations, starting as a console-based Java app, then a flash version, then a more-compatible HTML and JavaScript version that would even run on Internet Explorer 6.

FirstDose was an HTML and JavaScript, fully client-side dose calculator used to recommend first and subsequent doses before concentration measurements become available for dose adjustment. It used published models for vancomycin, amikacin and gentamicin accounting for covariates such as height, weight, post-menstrual age, renal function and certain concurrent treatments. It was designed to be simple to use, simple to understand, and easily accessible from any computer on the ward.

We conducted a small clinical trial in paediatric and neonatal intensive care units in Auckland, and learnt valuable lessons regarding useability, software compatibility and communication with hospital staff. People use software differently and there was a need to anticipate unexpected input and guide users accordingly. Of significance, users were more interested in learning how to improve dosing once concentration measurements became available, so we began work on NextDose.

NextDose would use Bayesian methodology to make the best use of information available for target concentration intervention. It would need a database to keep track of patients, plus a focus on security, stability and collaboration between team members

from different locations. Thanks to lessons learnt from FirstDose, initial development took place over just a few months before bringing to the hospital for initial evaluation.

NextDose launched as a browser-based web app with published models of busulfan, methotrexate and tacrolimus. It provides a relatively intuitive graphical user interface that drives a PHP server-side backend that communicates with NONMEM.

Dosing in the seriously ill is usually involves a multidisciplinary team, so NextDose is a collaborative tool, providing a common interface for all those involved in target concentration intervention and allows input from different locations at different times.

Today the development version of NextDose includes 11 medicines (busulfan, methotrexate, tacrolimus, warfarin, linezolid, voriconazole, gentamicin, amikacin, vancomycin, caffeine, mycophenolate) and has academic users around the world (NextDose n=295 , dev.NextDose n=122). The clinical version of NextDose has been used to guide dosing of busulfan in children (n=77) and adults (n=90) in Auckland Hospital since 2012.

Future work in Auckland: procalcitonin in healthy and infected neonates to inform PKPD disease progression modelling

January 15, 2019

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Presentation type Oral

Presenters Jacqueline Hannam

Appropriate antimicrobial therapy in neonates and babies is complicated by pharmacokinetic (PK) changes with age, body size and disease. Additionally we lack pharmacodynamic (PD) measures to gauge patient response. A correlation exists between elevated concentrations of procalcitonin (PCT) and infection +/- sepsis butmultiple other factors also contribute to PCT fluctuations (1, 2). For example, PCT concentrations are altered with trauma, surgery, burns, acute kidney injury, respiratory distress syndrome, haemodynamic failure, factors relating to birth including preterm delivery, maternal chorioamnionitis, low APGAR score at delivery, low birth weight and others (3-7). A normal time course of PCT elevation followed by return to baseline concentrations has been shown to occur in healthy neonates over the 48 h following birth (8, 9), and this differs in low birth weight infants (6). Consequently, the time course of PCT in neonates is complex, measurements are unsurprisingly variable and they can be difficult to interpret in the context of multiple patient factors.

Current dosing regimens for antibiotics are empirical with little integration of PK or PD knowledge, based instead on exceeding a minimum inhibitory concentration determined in laboratory cultures incubated for 48-72 h with drug concentrations selected at 2 fold increments. PCT measurements may provide a useful surrogate marker of drug response during infection that can be incorporated into these models to describe the time course of both infection and infection resolution with antibiotic therapy. Future work at Auckland will focus on establishing a dataset for PCT concentrations in healthy and infected neonates, as well as adults, from prospective data collection and collaboration with other centres, for the purposes of disease progression modelling and antibiotic therapy.

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Predictive performance of a Bayesian forecasting software for tacrolimus in adult heart transplant

January 6, 2019

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Presentation type Oral

Presenters Ranita Kirubakaran

Introduction: Previous clinical audit of tacrolimus (TAC) in 2017 heart transplant (HTx) recipients at St Vincent's Hospital, Sydney (SVH) observed poor sampling time of TAC trough concentrations. Bayesian forecasting software may assist in the interpretation of TAC concentrations collected at any point in time.

Aims: To evaluate the predictive performance of a Bayesian forecasting software, DoseMeRx® (Brisbane, Australia) in predicting oral immediate-release TAC concentrations immediately post-HTx at SVH.

Methods: A retrospective observational study of all HTx recipients (1 Jan – 31 Dec 2017) treated with TAC at SVH was conducted. Data inputted into DoseMeRx® included TAC concentrations and dosing regimen, and patient parameters such as age, gender, height, weight, haematocrit and CYP 450 3A5 genotype (if available).The predictive performance of DoseMeRx® was evaluated by comparing the predicted concentrations to the observed concentrations using median prediction error (MPE, a measure of bias) and median absolute prediction error (MAPE, a measure of precision). Clinically acceptable bias was between -15% and 15% while clinically acceptable precision was ≤20%.

Results: There were 38 HTx recipients, 25 (66%) males and a median (range) age of 56 (21-69) years. All patients received itraconazole 200 mg BD as a prophylaxis for invasive fungal infection immediately post-HTx for 6 months. During the first 3 weeks of TAC therapy, 328 blood concentrations were measured with a median (range) of 11 (2 – 19) samples per patient. DoseMeRx® under-predicts TAC concentrations for the first 2 weeks of TAC therapy. The software was robust from day 11 of therapy: bias was not

significant with clinically acceptable bias. DoseMeRx® displayed clinically acceptable precision from day 9.

Discussion: Preliminary assessment of DoseMeRx® immediately post-HTx highlighted accuracy in predicting TAC concentration from day 11. The improvement in MPE and MAPE over a week aligns the delay in the attainment of steady-state due to drug-interactions between TAC and itraconazole. Further assessment of the predictive performance of DoseMeRx® upon itraconazole cessation after 6 months of therapy is required.

A quantitative systems pharmacology model for glutathione depletion during paracetamol overdose

January 6, 2019

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Presentation type Oral

Presenters Jingyun Li

Introduction: Paracetamol toxicity is a common cause of acute liver failure in many countries. Most paracetamol is metabolised to the non-toxic sulfate and glucuronide conjugates. Only about 5% is oxidised to the highly reactive toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which can be detoxified by hepatic glutathione(GSH). At higher doses of paracetamol, NAPQI depletes stores of both GSH and cysteine. Hepatic necrosis is observed when GSH consumption is over 70%. As the limiting precursor for GSH synthesis, cysteine can be produced either by the degradation of GSH or the methionine cycle. Therefore, understanding the profile of GSH and methionine is critical to predict paracetamol-induced hepatotoxicity.

Objectives: The aim of this work is to understand GSH depletion and recovery under both therapeutic and overdose conditions.

Methods: We constructed a schema of a quantitative systems pharmacology (QSP) model for paracetamol metabolism. A component of this was available as a previously published mathematical model[1]. The model was modified to accommodate: (1) a non-specific tissue distribution compartment for paracetamol; (2) the irreversibility of paracetamol-protein adduct formation; (3) expansion of the GSH compartment to include the methionine cycle and trans-sulfation; (4) a positive feedback to increase the utilization of methionine(an essential amino acid) when GSH is depleted. The final model consisted of 31 states. The profile of the concentrations of plasma paracetamol and its sulfate and glucuronide conjugates after 20 mg/kg oral administration were compared against published results. The depletion profile of liver GSH was explored under different dose levels, 0 g, 1 g, 5 g, 10 g, 15 g and 20 g. Two mechanisms were proposed for investigating GSH depletion: (i) a reduction in oral intake of methionine and (ii) a positive feedback from GSH to methionine. All simulations were conducted in MATLAB 2017.

Results: The model simulation results for paracetamol and its metabolites in plasma matched the published results. The nadir of depletion of hepatic GSH decreased with higher paracetamol doses. In the absence of mechanism (i) or (ii) GSH recovered while paracetamol concentrations remained high. After including either mechanisms, about 70% of GSH is consumed by NAPQI after 10 g dose. Over 90% of GSH is depleted after 15 g and 20 g doses and did not recover to above 30% of normal GSH concentration after 50 hours. Even for a therapeutic dose, GSH consumption occurs but not to a critical value. When the input of methionine is turned off (mechanism ii), the profile of GSH concentration reaches a new paracetamol-dose-dependent steady state with a recovery based on the resumption of diet.

Conclusion: Our simulation results are consistent with the observation that a single dose of more than 10 g (or 150 mg/kg to 200mg/kg) may be associated with significant depletion of GSH and therefore the potential for liver toxicity. In addition, prolonged depletion of GSH to less than 30% of normal after paracetamol doses of 15 g and 20 g indicates that hepatocyte injury may be ongoing after the initial acute overdose stage. The mechanism of GSH depletion remains unknown. This work is the first step in understanding GSH depletion and potentially cysteine supplementation.

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An ePKPD model for sodium nitroprusside in adolescents

January 6, 2019

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Presentation type Oral
Presenters Salma Bahnasawy

Background: Sodium nitroprusside (SNP) is commonly used to control blood pressure (BP) in children during surgery. Recently, the results from a clinical trial in children using SNP during surgery were used to develop a KPD model to help guide the dosing of SNP in this population. [1] The model revealed that there were two subpopulations of patients who have different sensitivities to SNP, but no correlations between the subpopulations and covariates were found. An extended PD (ePD) model of the haemodynamic system has been developed previously and contains appropriate control and feedback mechanisms. [2] This model was recreated and combined with a PK model for SNP and different pharmacological targets within the haemodynamic system were created and tested for effects comparable to the data.
Aim: The aim of this work is to develop an ePKPD (i.e. “semi-mechanistic”) model that can be used to describe the haemodynamic profile in adolescents upon infusion of SNP and test different suggested mechanisms for the effect of SNP.

Methods: The data arose from 88 adolescents and young adults, who were 13 years and over. The dosing of SNP was titrated in each subject to a predefined target mean arterial pressure ‘MAP’. If the MAP was too low then the subject was discontinued from further dosing. A model describing the haemodynamic responses (MAP, systolic blood pressure ‘SBP’, diastolic blood pressure ‘DBP’, and heart rate ‘HR’) was recreated in MATLAB. Different targets of drug action were identified in the model that could be used to modulate the effect of SNP. The two main targets were; (a) decreasing the peripheral resistance (PR), and (b) baroreceptor resetting. A simplified PK model for SNP was then added to the model. Three different scenarios for SNP mechanism of action were considered in the various model expressions; (a) affecting PR only, (b) affecting baroreceptors only and, (c) affecting both PR and baroreceptors (i.e. combined mechanism). Model PD parameters and baseline values for the haemodynamic variables were calibrated to the same initial values as the observed

data. The model predictions (at a single SNP dose) were then overlaid on the data. No dose titration was performed based on model predictions.

Results: The overlaid profiles for model predictions and observed data show that the model can describe the central tendency of the data and that it can be used to evaluate the different mechanisms that were hypothesised about SNP mechanism of effect. For the PR only mechanism, the model underpredicts MAP, SBP, & DBP at the early phase before reaching the steady state (SS) and overpredicts the SS level of HR. The baroreceptor resetting mechanism underpredicts the whole profile of HR. The combined mechanism was most flexible and aligned with the observed haemodynamic variables.

Conclusion: The results suggest the mechanistic plausibility of the proposed model, as reflected by the consistency of the model predictions with the observed data. Since the current data contains multiple dose titration steps in each individual including discontinuation of treatment, the next step requires the data to be modelled.

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Implementation of an approximate input forcing function for modelling single tissues in the Open Pharmacology Suite

January 10, 2019

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Presentation type Oral

Presenters Jim H. Hughes

Objectives: The PK-Sim®software is used for the development of whole-body physiologically-based pharmacokinetic (PBPK) models. During model development parameters for drug disposition must be provided, often sourced from *in vivo/in vitro* experiments. If these parameters are influential, misspecification in a single organ can impact the entire PBPK model. Through development of single-tissue models, initial estimates for influential parameters can be determined in a simpler environment. This study aimed to develop a method using the Open Pharmacology Suite (containing PK-Sim®and MoBi®), which allows for the development of single-tissue models.

Methods: A method was developed in MoBi®that uses models developed in PK-Sim®and converts them into single-tissue models. It uses curve fitting equations as a forcing function, which is then corrected to account for changes caused by step-wise integration during simulation. This method was evaluated to ensure that tissue concentrations of single-tissue models closely represent the whole-body model tissue concentrations that they were based on.

Results: The forcing functions used by the method were found to be accurately implemented, with tissue concentrations of most single-tissue models being representative of those in the whole-body model. Single-tissue models that were not representative of the whole-body model, had a constant proportional error over time. These errors were corrected using a scaling factor on observed concentrations during parameter identification.

Conclusions: The method presented provides a single-tissue development workflow for use with PK-Sim® model development. Once the method has been implemented in

model, it can easily be reused in subsequent models to enable the estimation of better initial estimates for whole-body models.

Investigating the pharmacokinetics of snake venom – a cocktail of toxins

January 6, 2019

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Presentation type Oral
Presenters Suchaya Sanhajariya

Background: Snake venom is a mixture of protein-toxins, which can cause a range of biological effects. The protein components in snake venom have molecular sizes ranging from 4 kDa to 150 kDa and are expected to exhibit different pharmacokinetics (PK) profiles. Therefore, the phenomenological appearance of plasma snake venom concentrations is governed by the combination of disposition processes inherent to each protein component. Understanding the influence of the PK of each molecular weight fraction on the overall venom PK can improve our understanding of the individual toxin PK profile and help identify how venom PK can be influenced by the composition of the dominating proteins.

Aims: This study aims (1) to determine the effects of different molecular weight proteins on the time course of the snake venom, and (2) to determine the ability to identify toxin profiles based on their integral only.

Methods: The relationships between proteins of variable molecular weights and their clearance (CL) and volume of distribution (V) were investigated and found to follow a simple log-linear relationship. Both aims were addressed using a stochastic simulation estimation (SSE) study using MATLAB for simulation and NONMEM for estimation. Sixteen variations of venom comprising two to nine toxins of variable molecular weights were investigated. Each venom variation was evaluated in a SSE study involving 100 virtual patients with a rich sampling scheme. The prior population values of CL and Vfor each molecular weight toxin were generated from a distribution based on their molecular weight. Individual values of CL and V were simulated from the population values assuming an exponential between subject variability model and a combined residual error model was used to generate the data. The venom data were modelled as the sum of each toxin data under three scenarios: (i) an intravenous (IV) bolus 1-compartment model using the population parameter estimates without uncertainty in the prior [perfect case], (ii) an IV bolus 1-compartment model using population parameter values generated from the prior including uncertainty [best field case], and (iii) a first-order

absorption 1-compartment model with population parameter values generated from the regression model with uncertainty [likely field case]. The venom concentration-time course was modelled using 1- to 9- compartment models. Akaike information criterion (AIC) was used as a basis for model selection.

Results: The concentration-time data of sixteen venoms were best described by 2- to 3-compartment model in all three scenarios. Data from venoms comprised of two compounds favoured a 2-compartmental fit, over a 1-compartmental fit. Data from venoms comprising more than 4 components seldom preferred more than a 3-compartment model. In scenario (i), data of all venoms that comprised of three or more compounds were best described by a 3-compartment model. In scenarios (ii and iii), where uncertainty was incorporated, data of venoms with three or more components were best described by 2- or 3- compartment models. Despite venoms comprising more than 3 toxins of various molecular sizes and PK characteristics, we can observe no more than 3-compartmental behaviour.

Conclusion: A population pharmacokinetic analysis of venom data does not support the identification of more than a three-compartment profile. This indicates that it is not possible to determine the toxin profile of venoms based on measuring whole venom only, except in circumstances where there are a minor number of highly expressed determinants.

An extension of Janmahasatian's fat-free mass model to incorporate differences due to ethnicity

January 6, 2019

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Presentation type Oral

Presenters Jaydeep Sinha

Introduction: Janmahasatian's [1] model for fat-free mass model (FFM_{Jan}) was developed based on a population that descended from European ancestry. There is some evidence that humans from different ethnic backgrounds may have different body composition based on standard phenotypic characteristics (e.g. sex, weight and height) and hence the model may not predict well into these groups. In particular, the model is known to over-predict (FFM_{Jan}) in Indian patients [2]. Therefore, there is a need to extend Janmahasatian's model in a mechanistic way in order to accommodate ethnicity specific deviations, should they exist. This would enable application of the model to other populations when data have been collected.

Aim:
*Part-1:*To derive an extended version of Janmahasatian's *FFM* model structure (FFM_{Ext}).
*Part-2:*To apply the extended *FFM* model to an Indian population ($FFM_{Ext(Ind)}$).

Method: *Part-1:*A primary assumption in Janmahasatian's derivation is a proportional relationship between bioimpedance (*Z*) and density. This can be relaxed by allowing either a different proportional relationship (e.g. due to different composition of biomaterials, but relatively constant to density alteration) or a nonlinear relationship (e.g. due to variable composition with respect to density alteration) which may more readily reflect the composition in different ethnic groups. This was achieved by incorporating correction factors Ψ {Ψ_1, Ψ_2, Ψ_3} to the existing *Z* model parameters. *Part-2:*Individual data of age, sex, height, and weight of 100 adult Indian medical patients was obtained from PSG Hospital, Coimbatore, India. Individual *FFM* data calculated by Kulkarni's model (FFM_{Kul}) [3] was used as the dependent variable (DV), and the Ψ parameters of the FFM_{Ext} equation were estimated to develop the model for $FFM_{Ext(Ind)}$ using NONMEM (version 7.3). A combined error model was used to account for the residual error. A visual plot of observed (DV) vs. predicted *FFM* was used to evaluate the $FFM_{Ext(Ind)}$ model.

Results: The full extended model is given in Eq 1 and 2, where Ψ = 1, for all elements of Ψ representing the European population and we propose these elements can be estimated when considering data from other ethnic groups. For part 2, the estimate of Ψ_1 was 0. The value of Ψ_2 (a proportional term) was 0.75 (RSE: 2.4%) for males and 0.68 (RSE: 2.5%) for females respectively, and Ψ_3 (a nonlinear term) was not influenced by sex and was 0.71 (RSE: 1.0%). Note, for the Indian population the first term of the denominator drops.

For males:	$$FFM_{Ext} = \frac{9270.WT}{\psi_1.216.BMI + \psi_2.6680.BMI^{(1-\psi_3)}}$$	(1)
For females:	$$FFM_{Ext} = \frac{9270.WT}{\psi_1.244.BMI + \psi_2.8780.BMI^{(1-\psi_3)}}$$	(2)

Conclusion: This work further supports the applicability of Janmahasatian's model to populations other than what it was developed from. For this purpose, ethnic specific correction factor(s) need to be estimated and has been illustrated for Indian people in this work.

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Evaluation of the fingerprint profiles of the cannabinoid-1 receptor signalling via a kinetic modelling approach

January 6, 2019

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Presentation type Oral

Presenters Xiao Zhu

Introduction: Biased agonism (aka ligand bias) is a term that is used to describe the ability of ligands to differentially regulate multiple signalling pathways when coupled to a single receptor. Quantification of ligand bias is critical to lead compound optimisation. Signalling is affected by rapid ligand-mediated receptor internalisation. Hence, the conventional use of equilibrium models is not applicable as (i) receptor numbers vary with time and (ii) some kinetic profiles show non-monotonic profiles over time. A joint kinetic model is required to quantitatively assess the time-dependent modulation of the cannabinoid-1 (CB1) receptor by ligands and provide novel insights into the complex interplay among ligands, receptors and pathways.

Aims:

1. To develop a kinetic model that describes three signalling pathways (pERK, forskolin-induced cAMP signalling, and internalisation) coupled to the CB1 receptor.
2. To visualise fingerprint profiles of bias of the CB1 ligands.

Methods: Data were available from internalisation, cAMP and pERK pathways of the CB1 receptor under multiple concentration levels of six CB_1ligands: CP55940 (CP), WIN55212-2 (WIN), anandamide (AEA), 2-arachidonoyl glycerol (2AG), Δ^9-tetrahydrocannabinol (THC), BAY59-3074 (BAY). A mechanism-based stimulus response model was developed using NONMEM to describe the time course of three pathways sequentially using a PPP&D modelling framework. Internalisation was described by a target-mediated drug disposition model with a quasi-steady state assumption. pERK and cAMP were both described by a stimulus response model linked to the constitutive activity of the pathway. Ligand bias was determined by (1) normalising ligand specific metrics (*e.g.,* ligand-mediated internalisation rate constant

and ligand intrinsic efficacies for cAMP and pERK pathways) to the reference ligand, and then (2) further normalising it to a reference pathway (internalisation). This double normalisation provides the standard metric used in pharmacology to describe ligand bias. The ligand bias profiles were visualised in a radar plot.

Results: The developed model adequately described the signalling profiles of the CB1 receptor. All model parameters were precisely estimated (<50% relative standard error). The ligand-mediated internalisation was more than 10 fold faster than constitutive internalisation. The constitutive internalisation rate constant was typically 0.0016min^{-1}(16% RSE) and ligand-mediated internalisation rate constant ranged from 0.028 to 1.11 min^{-1}. For the pERK pathway, the estimated system maximal stimulation was 56 fold over baseline (24% RSE). The estimated duration of stimulation was 3.76min (3% RSE), which was consistent with observed peak time (from 3 to 5 min). For the cAMP pathway, the estimated system maximal inhibition was 0.76 fold over baseline (5% RSE). From visualisation of the ligand bias profiles, two biased ligands (WIN and 2AG) were identified that displayed higher selectivity towards the cAMP pathway.

Conclusion: This is the first report of a full kinetic analysis of CB1 system under non-equilibrium conditions. The kinetic modelling approach is a natural method to handle time-varying data when traditional equilibria are not present and enables quantification of ligand bias.

Evaluation of study designs to test the intact nephron hypothesis

January 6, 2019

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Presentation type Oral

Presenters Sudeep Pradhan

Introduction: Renal dose adjustment generally assumes a linear relationship between renal drug clearance (CL_R) and glomerular filtration rate (GFR). The theory underpinning this practice is the Intact Nephron Hypothesis (INH) [1]. A recent review by our group suggested that the INH may not be a suitable general model for renal drug clearance, particularly for drugs that are clearly largely by tubular secretion where a non-linear relationship between CL_R and GFR is expected [2]. To date, the study designs required to detect a deviation from the INH in renal drug studies have not been explored.
Aim: To evaluate Phase 1 renal drug study designs recommended by the United States Food and Drug Administration (FDA) [3] and the European Medicines Agency (EMA) [4] for testing the INH.

Methods: The FDA and the EMA guidelines for Phase 1 pharmacokinetic studies in patients with renal impairment were evaluated for their performance to discriminate between linear (under INH scenario) and nonlinear (under non-INH scenario) relationship between CL_R and GFR, when latter was true. The key difference between the two guidelines is the recommended method for estimating renal function. The FDA recommends a serum creatinine based equation for estimating GFR (eGFR) and the EMA recommends using an exogenous marker for measured GFR (mGFR). Two models were proposed to describe the relationship between CL_R and eGFR or mGFR:

1. M1: a linear model based on the INH scenario
   CLR= THETA(1) * GFR
2. M2: a nonlinear model based on the non-INH scenario
   CLR= THETA(1) * GFR ^ THETA(2)

where, GFR is either eGFR or mGFR for the FDA or EMA guidelines, respectively; THETA(1) is the linear coefficient parameter and THETA(2) is the exponent parameter.

A series of stochastic-simulation and estimations were conducted to assess the performance of the designs based on the FDA and the EMA guidelines in terms of their

ability to identify a departure from the INH. The number of subjects for each simulated study was n = 4, 8, 12, 16, 20, 24, 48, 72, 120, 240, 480, 1080. The studies were replicated 1000 times. Alpha-error, power, relative standard error (RSE) and bias were calculated to assess the designs based on the FDA and the EMA guidelines.

Results: Study designs under the EMA guideline with ≥ 8 subjects had power ≥ 80% to correctly detect non-linear relationship between $CL_R$and GFR. Under the FDA guidelines, ≥ 80% was achieved only with ≥ 24 subjects. For M2, the true model, the RSE of THETA(1) was < 17% for all designs with power ≥ 80%, while TEHTA(2) was not precisely estimated with an RSE of 59. To achieve RSE of < 25% for THETA(2) at least n=48 and n=72 subjects were required for designs under the EMA and the FDA guidelines, respectively. The estimated parameters for all the tested designs with power > 80% were unbiased.

Conclusions: The present study evaluated the designs recommended by the FDA and the EMA guidelines for testing the INH. The FDA guideline would require 3 times more subjects to achieve ≥ 80%power to detect non-linear relationship between $CL_R$and GFR compared to the EMA design. Under non-INH scenario, with number of subjects recommended by the EMA guidelines (n = 24), designs under both the guidelines would will not be able to estimate the parameters precisely and therefore will be unlikely to establish the true relationship between $CL_R$and eGFR or mGFR.

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Extrapolation of acetaminophen PK models from adults to paediatricians

January 15, 2019

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Presentation type Oral

Presenters Harvey Ho

Extrapolation of PK models from adults to paediatricians requires re-qualification of physiological and pharmacokinetic parameters. Specifically, maturation of metabolism pathways, urinary clearance and rapid weight changes in paediatricians affect PK profiles. In this presentation we describe a case study of extrapolating a clinical acetaminophen (APAP) PK model from adults to neonates (<28 days) and infants (29 days – 1 year). The PK model consists of two compartments (blood and urine) with Michaelis-Menton equations describing the glucuronidation, sulfation and oxidation reactions, and linear functions for recovery of metabolites in urine. The parameters used in the validated adult PK model are re-assessed in the paediatric PK model using a Latin hypercube method. Furthermore, a virtual population trial on 200 subjects are run using the Monte-Carlo method. The model is then qualified against published *in vivo*, *in vitro* and *in silico* studies of APAP PK. Such a model practice, after validated with clinical data, could provide a useful computational workflow as the first step in PK model extrapolation from adults to paediatricians.

How many NMLE articles are published in higher Impact Factor clinical journals?

January 12, 2019

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Presentation type Oral

Presenters Stefanie Hennig

Background: Pharmacometrics aims to understand the drug-patient interaction, connects various fields such as physiology, pharmacology, pharmacotherapy, clinical pharmacy, mathematical modelling, statistics, systems biology, pharmacokinetics/-dynamics in a coherent framework to improve drug development and patient therapy outcomes. The aim of this review was to identify publications that have applied the nonlinear mixed effects (NLME) modelling approach since its first appearance in 1980, and have been published in high impact clinical journals.

Methods: The search terms “nonlinear mixed effect modeling” OR “nonlinear mixed effect modelling” OR nonmem OR monolix OR pharmacometric* were used to search three databases (Pubmed, Web of Science and Embase) for articles published in English between 1980 and August 2018 (time of the search). Journal impact factor were identified via Web of Science or the journal’s webpage and recorded as per October 2018.

Results: 10,893 articles were identified; after duplication were removed and titles and abstracts were scanned 4,387 articles remained. A continuously increasing number of articles were published in 578 unique journals with 51% of articles published in 11 journals. Articles identified were published in journals with impact factors ranging from 0.1 to 26.3 (Journal of Clinical Oncology). The median impact factor was 3.08. 10.6% articles are published in journals with no impact factor. 2.2% of articles applying or developing methods in the field of NLME are published in Journals with IF> 6. Over 64.9% of articles had a first/corresponding author from academia, 27.7% from a hospital and 7.4% from industry. The most common author teams were academics and clinicians (38.1%) followed by academics and authors from industry (14.9%). When published, presentation of the methods used and the description of the results was seldom according to standards. [1, 2]

Conclusions: Communication of the impact of the results arising from NLME studies needs to improve, peer-review within the area need to increase outside the academic setting and engagement with statistician and clinicians need to improve.

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Analyzing endpoints with many ordered categories: theory and applications

January 6, 2019

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Presentation type Oral

Presenters Chuanpu Hu

Background: Longitudinal exposure-response (E-R) modeling of clinical endpoints is important in drug development to identify optimal dose regimens. Clinical endpoints are often ordinal composite scores. Typically, endpoints with few (e.g., <6) categories are analyzed as categorical, and endpoints with many (≥10) categories are analyzed as continuous. Endpoints with many categories often show skewed distributions that require special handling. The bounded outcome score (BOS) approach emerged in the last decade aims to parsimoniously model endpoints with moderate to large number of categories, and has been put under a general ordinal data analysis framework [1]. Most recently, benefits of the categorical analysis approach have been argued even in situations with many categories [2].

Objective: To provide an overview of the analysis approaches, discuss developments up to date, and facilitate an understanding of when best to use what approaches in the context of longitudinal E-R modelling of clinical endpoints with many categories.

Methods: Under the unifying statistical framework [1], theoretical characteristics of BOS [3] and categorical analysis approaches are discussed. The ability of these approaches in describing and predicting the endpoints of interest are compared with the continuous analysis approach though some recent applications [2]. The implications on dosing regimen selection are discussed.

Results: The continuous analysis approach requires symmetric distributional assumptions, and suitable transformations are often difficult to find for clinical endpoints that show skewness. BOS approaches may be parsimonious but often lead to significant biases in predicting derived endpoints, e.g., responder/non-responder rates based on the clinical endpoint. The ordered categorical analysis approach has appealing theoretical characteristics, and may work well with sufficient sample sizes, e.g. as in phase 3 clinical trials. Impact of the appropriateness of E-R analysis approach can be significant, e.g., those used for phase 3 dose selections may lead to the difference of with or without post-marketing requirements at the approval stage.

Conclusion: Appropriate analysis approach for clinical endpoints with many categories require careful considerations and may or may not need to be technically complex. Important influential factors include characteristics of the endpoint, whether any additional derived endpoints are of interest, and sample size. The analysis choice may directly impact clinical dosing decisions where the stakes are high.

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Dose banding- weighing up benefits vs risks

January 6, 2019

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Presentation type Oral

Presenters Stephen Duffull

Background: Dose banding is the allocation of patients into a pre-specified dose group based on the patient's value of a covariate and is commonly recommended in drug labels. The simplest form of dose banding assigns all patients to receive the same dose irrespective of their characteristics. The corollary to "one dose fits all" is where each patient is essentially their own dose group (i.e. a continuous dose adjustment, e.g. mg/kg of body weight). The benefits of dose banding is the simplicity for adjusting doses based on a patient's characteristics, for instance all patients with eGFR > 30 ml/min might be recommended to receive the same dose and those less than 30 to receive a different (or no) dose. There are two main issues with dose banding: (1) dose banding results in loss of granularity in dosing by applying a discrete set of doses rather than selecting from a continuous dose range which may reduce the probability of success and (2) patients may be harmed if they have a set of characteristics that is just above or below the dose banding cut-off such that they receive an increased dose or reduced dose, respectively.

Aims: This study aims to (1) determine the influence of dose banding vs "one dose fits all" vs continuous covariate based dosing on probability of target attainment (i.e. success), (2) explore optimisation of dose banding on the probability of study success, (3) determine the characteristics of optimising dose banding to reduce harm for those at the dose banding cut-point and (4) define a utility that maximises success while reducing harm.

Methods: The aims were addressed by a simulation study using a simple pharmacokinetic application. The model was a 1-parameter steady-state model defined by the parameter CL (mean=1 L/h, CV%=30) and dose (1 mg). An influential covariate with positive linear correlation (Z; mean=1, CV%=30) was chosen. Success (target attainment) was determined as a steady-state concentration of between 1 and 2 mg/L. Harm was determined using a linear loss function associated with the distance of the predicted concentration from the target for subjects that had a covariate value that was just above or just below the dose band cut-off. All simulations were performed using MATLAB. Optimisation was performed using a global adaptive random search.

The following scenarios, relating to the 4 aims were considered. The design consisted of the dose banding cut off (i.e. the value of the covariate at which the dose would be changed) and the value of the dose for the band just below the cut off and above the cut off. The following simulations were constructed (i) the probability of target attainment for "one dose fits all" [aim 1], (ii) the probability of target attainment for a continuous covariate based dosing regimen [aim 1], (iii) the optimal banding for target attainment with 2 or more dose levels [aim 2], (iv) the optimal banding for minimising harm for patients at the cut-off value of Z [aim 3] and (v) the performance of a utility that balances success against harm [aim 4].

Results: The lowest success is seen with a "one dose fits all" scenario and for (i) an optimal dose of 1.3 mg provided a probability of target attainment of 0.59. In contrast a dose that is based continuously on the covariate Z (ii) yielded a success of P=0.72. Optimising the probability of target attainment with two dose levels yielded (iii) a dose band cut-off at the 52th percentile of the covariate Z and dose levels of 1.1 and 1.8 mg. To minimise harm (iv), i.e. the loss associated with being dose reduced at the cut-off value of Z, then the best harm aversion method was to revert back to "one dose fits all". During the search either the dose for each dose band were the same or the cut-off value of Z went to the extrema (e.g. 100thpercentile). Finally a linear utility of both probability of target attainment and the loss associated with harm resulted in (v) a narrowing of the differences between the two dose levels. The dose band cut off was lower at the 36thpercentile of Z and the dose values were 1.1 and 1.3 mg.

Conclusion: Exploring dose banding, using a simple pharmacokinetic model, showed a clear benefit of continuous covariate based dosing for achieving success. Dose banding can be optimised to achieve higher success rates of attaining the target, but this also increases the risk of harm to patients at the cut-points. If dose banding is to be considered then consideration of both target success as well as loss associated with dose adjustment need to be considered on a case by case basis.

Parameter Analysis for PBPK Model for Enalapril

January 15, 2019

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Presentation type Poster

Presenters Zhe Yang

Physiologically based pharmacokinetic (PBPK) modeling is valuable for drug development (Phase I). While PBPK models may share similar compartmental structures (e.g., blood, liver) for different species, a distinct set of physiological (e.g. compartmental volume and blood flow rate) and drug-specific (e.g. metabolism and clearance rates) parameters need to be used in different species. However, it is still difficult to obtain some of these parameters from in vivo or in vitro experiments. Hence, to predict and verify the effect and accuracy of those parameters through parameter analysis is often the only choice.

In this work we investigate the clearance PBPK model of Enalapril, a hypertensive pro-drug hydrolyzed to Enalaprilat, which is an Angiotensin Converting Enzyme (ACE) inhibitor that prevents ACE from transforming angiotensin I into angiotensin II. We extrapolate a validated PBPK model of Enalapril from the rat hepatic system to human beings. At first, we list all physiological and pharmacological parameters used in the system and justify whether a parameter extrapolation is qualified. Then, we use a parameter analysis method (Latin Hypercube that probes 1/10 to 10 fold of a predicted parameter) for those parameters, which are not obvious and may impose a direct effect on the model (e.g., metabolism/biliary clearance rate). Furthermore, we use the Monte-Carlo Method to simulate the time course of enalapril from 100 virtual subjects, which illustrate the range of PK profiles in humans.

The models are developed in Matlab, and also CellML/OpenCOR. The simulation results are compared with published data from clinical trials. In conclusion, a population PBPK model for humans has been extrapolated from a rat PBPK model for Enalapril. The physiological and PK parameters have been re-adjusted to yield the clearance ratio in humans, which is similar between these two species despite the drastic weight difference (the weight of the human is almost 250 times that of the rat).

PBPK modeling for lindane across different species

January 15, 2019

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Presentation type Poster

Presenters Shengjie Zhang

Interspecies differences are one of the important factors to consider when extrapolating a physiologically based pharmacokinetic (PBPK) model from one species to another. As some of the parameters used in PBPK models are not always available from in-vitro/in-vivo experiments or previous literature, it is important to know how to estimate the parameters from one species to another based on some known relationships. Lindane is a neurotoxicant and has been used as pesticides. It impairs neuronal firing rate, so the concentration in the body becomes important to know. Although it has been banned since 2009, there are still residues remain in the environment and may be accidentally administered by farm animals. In this study, lindane is used to extrapolate rat and human PBPK model to a cow model to estimate the concentration of lindane in several compartments (liver, blood, rapidly perfused tissues, slowly perfused tissue, mammary tissue, adipose tissue and brain) in cow after a single dose of lindane.

Rat model and human model used for extrapolation are adopted from previous studies. The model predicts the concentration of lindane in tissues during the elimination process. The administrations of lindane were considered as an oral dose. Parameter analysis was done using MATLAB to check if the parameters and the result of the cow model are within an acceptable range. The concentration of lindane within each compartment in the cow is similar to that of human and rat even though some of the physiological parameters such as body weight and cardiac output are significantly different. The model result was compared with several previously published data in rats, human and cow. This finding indicates that the model can be predictive for lindane elimination in cows.

As lindane is a lipophilic pollutant, further modifications of this model from single administration to chronic low dose administration can be used to predict the accumulation of lindane residue in the body.

Pharmacodynamic effect of evogliptin on bone metabolism in healthy menopausal women

January 10, 2019

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Presentation type Poster

Presenters Namyi Gu

Background: DPP-IV has a role in degradation of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), and gastric inhibitory polypeptide (GIP) which had been reported to reduce bone resorption. We investigated the pharmacodynamic effect of evogliptin, a DPP-IV inhibitor, on human bone metabolism in human using serum carboxy-terminal collagen crosslinks (CTX) as a biomarker of bone resorption.

Method: This study was designed as a single institution, one sequence, single-dose, baseline comparative clinical trial. Serial blood samples were collected to quantify the concentrations of CTX), intact GIP, intact GLP-1, total GLP-2, PTH, osteocalcin were collected on Day 1 (baseline measurement day) and Day 2 (treatment day) during admission period. Urine samples for the quantification of deoxypyridinoline (uDPD) and creatinine (uCr) were also collected during the study. Paired t-test and McNemar test were applied in the hypothesis tests with a significance level of 0.05.

Results: Twenty-two menopausal women were enrolled and twenty subjects completed the study schedule. Serum CTX concentration significantly decreased at 2-8 hours after drug administration. Plasma intact GIP concentration significantly increased at 2-14 hours after drug administration, while plasma total GLP-2 concentration significantly decreased at 4-8 hours after drug administration. The levels of plasma intact GLP-1, PTH, osteocalcin, and uDPD/uCr were not significantly different between Day 1 and Day 2.

Conclusion: The study results suggests that the degradation of GIP might be more influenced by the DPP-IV activity compared to GLP-1 and GLP-2, and bone antiresorptive effect of evogliptin might be related to GIP rather than GLP-1 or GLP-2.

PAGANZ Workshop: CellML and OpenCOR

January 15, 2019

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Presentation type Workshop

Presenters Soroush Safaei

Over the past 10 year quantitative systems pharmacology has become an integral part of pharmacometrics. While the models and methods used in a QSP framework are novel to pharmacometricians they have been well established in the disciplines of systems biology and bioengineering. Software (e.g. CellML, SBML, …) for specifying models and enabling simulations from models are also well established in other disciplines as well as methods for model verification and validation.

In this workshop, CellML will be explored using the OpenCOR interface and applied to two simple examples based on the PK and the PKPD of warfarin. This workshop expands on a previous PAGANZ workshop on CellML in 2011 in which the CellML language were introduced and its concepts were discussed. The purpose of this workshop is: (1) to provide attendees with an experience of using a model based mark-up language to specify models, (2) to illustrate how units of variables and parameters can be specified in a systems model and used to enforce mass balance, (3) to explore the use of a declarative language structure, (4) to be able to see how modularity can be built into systems models via the CellML language style, (5) to gain an appreciation of how CellML can be used to build models that encompass the features of reproducibility and reusability.