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DEVELOPMENT OF BAYESIAN AND NON-BAYESIAN
MELPHALAN PHARMACOKINETIC MODEL FROM
LITERATURE-GENERATED DATA

BY
ENOCH COBBINA

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
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IN
STATISTICS

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MASTER OF SCIENCE IN STATISTICS

OF

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ABSTRACT

Published articles constitute a huge repository of population pharmacokinetic (Pop PK) models that can be repurposed to answer dose-related questions. We present a Simulation-Informed-Statistically-Aided (SISA) method that can be used to select population pharmacokinetic models from literature for repurposing.

Seven published melphalan PK models, and 1 reference model from FDA NDA submission documents were selected. A 30 minute IV infusion of 140 mg/m² of melphalan was simulated using each of the 7 models. The predictive performance of each of the models were evaluated using a proposed method called modified standard normal deviate (mSND). Five models, M1, M3, M4, M5 and M6 performed well predicting the given dose with mSND within 0 -3. A composite dataset was generated from these 5 models and used to develop a composite melphalan PK model using First-order conditional estimation method with interaction (FOCE-I), and the Bayesian Hamiltonian Monte Carlo No-U-Turn Sampler (HMC NUTS) estimation methods. Both informative and weakly informative priors were tested during the Bayesian estimation.

For both Bayesian and Non-Bayesian methods, a two compartmental model adequately fit the composite data. The parameter estimates and the model predictions were in agreement with those from reference model. This confirmed that validity of SISA. Again, the findings suggested that literature data can be repurposed to develop composite PK models.

It is hoped that further refinement of this method will provide a more objective approach for selecting PK models for repurposing.

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CHAPTER 1

1 INTRODUCTION

1.1 Published articles constitute a huge repository of PK models

Published articles constitute a huge repository of population pharmacokinetic (Pop PK) models (Chen et al., 2018, Tsamandouras et al., 2017, Snelder et al., 2019, Xue et al., 2011, Nath et al., 2010, Lamba et al., 2010). This provides researchers with a ready and inexpensive source of models to answer dose-related questions, before further investigations in humans. Selection of Pop PK models from literature could however be challenging when you have multiple models to choose from. Direct comparison of the model parameters and study design alone do not offer an objective approach for selection. There is therefore the need to develop an approach that incorporates the model parameters and study design, and apply statistical methods to compare predictions of exposure after a single dose.

In this work, we present a simulation-informed statistically-aided (SISA) method that can be used to select population pharmacokinetic models from literature for repurposing.

1.2 Pharmacokinetic modeling and simulation (M&S) are important tools for drug development.

The cost of drug development is huge, about 1 – 3 billion dollars (DiMasi et al., 2016), and companies are pursuing various strategies to minimize it. Modeling and simulation is gaining a wide acceptance in drug development due to its potential to reduce the cost of drug development. With a single model, thousands of simulations may be performed *in silico* before actual experiments in animals or man. In addition to cost reduction, this approach reduces the number of participants and experiments to be conducted.

Pharmacokinetic modeling and simulation (M&S) is a powerful tool used by clinical pharmacologist to characterize the time course of drugs, and also to predict doses. Several clinical questions regarding dose and administration of drugs have been answered with simulations and confirmed with actual studies (Aarons et al., 2001).

Considering the number of PK models in literature, it may be prudent to repurpose published PK models than to develop new ones from the scratch. However, the selection of the model requires the consideration of multiple factors.

Firstly, there is the need to compare the subject population from which the PK model was developed. This may include gender, race, diseases, etc. Second, one may have to compare the design of the pharmacokinetic studies, and lastly the parameters from each model. This process is not easy to perform without a well-defined procedures.

To date, only an empirical approach is used. This approach uses the number of citations, relevance of population, or author reputation as criteria for selection of population PK models from literature. Whereas this is straight forward, it is biased and

might miss the opportunity of selecting the best model for use. A more objective criteria that combines study design and PK parameters would greatly enhance PK selection.

1.3 Melphalan pharmacokinetic model in literature

Melphalan was chosen for the purposes of this study because of the availability of multiple models in literature. It is an alkylating chemotherapeutic agent, and increasingly, it is gaining more acceptance as an important agent for the treatment of multiple myeloma (Martino et al., 2013, Kuhne et al., 2008, Mateos et al., 2015). This is due to its myeloablative effect, and availability in both oral (ALKERAN®) and intravenous (EVOMELA®) dosage forms.

1.4 Overall goal of this project

The overall objectives of this thesis are to:

1. Identify population pharmacokinetic models that characterize the disposition of melphalan in patients from literature.
2. Develop a criterion to guide the selection of melphalan models from literature.
3. Generate composite melphalan pharmacokinetic data from literature through simulation.
4. Develop composite population PK model for melphalan using Bayesian and non-Bayesian estimation methods.

CHAPTER 2

2 REVIEW OF LITERATURE

2.1 PHARMACOKINETIC CONCEPTS

2.1.1 Pharmacokinetics and the disposition of drugs

Pharmacokinetics is a term used in pharmacology to describe the processes of absorption (A), distribution (D), metabolism (M) and excretion (E). After oral or subcutaneous administration of a drug, it is absorbed into circulation, and may interact with blood components like albumin (Yamasaki et al., 2013). The remainder of the drug molecules unbound to blood components move into different body compartments, either passively by diffusion, or actively by transporters.

The fate of the drug in different body compartments is determined by the availability of enzymes (e.g. Cytochrome P450) (Guengerich, 1992), transporters (e.g. p-glycoprotein) (Nigam, 2015), and other physiological factors. The enzymes mediate the metabolism of the drug into a more soluble form. Both metabolized and parent drugs may be excreted from the body via the renal or biliary routes.

The skin and the gastrointestinal tract are the major sites of drug absorption after subcutaneous or oral administration respectively. The liver expresses many enzymes for metabolism, making it one of the most important sites for drug metabolism. The bile and kidney serve as key organs for the excretion of drugs from the body.

Quantitatively, absorption is described by the absorption rate constant (k_a) and the bioavailability fraction (F). The absorption rate constant describes the speed of absorption, whereas the bioavailability factor describes the extent to which an oral or subcutaneous dose is available to systemic circulation relative to intravenous administration. Similarly, distribution is described by the volume of distribution parameter (V), and elimination by the clearance parameter (Cl).

2.1.2 Population Pharmacokinetic (Pop PK) models

Population pharmacokinetic models describe the time course of drugs in the body. They provide mathematical and statistical description of the absorption (A), distribution (D), metabolism (M) and excretion (E) of drugs (Van Der Graaf and Gabrielsson, 2009). Pop PK models support the determination of doses for clinical trials, and provide a framework for evaluating factors that can influence the ADME processes. **Figure 1** summarizes areas where pharmacokinetic modeling and simulations are commonly used in drug development (Mould and Upton, 2012).

Figure 1. Modeling and simulation during drug development. Diagram was obtained from (Mould and Upton, 2012).

2.1.3 Pop PK models are non-linear mixed effects compartmental models.

Population pharmacokinetic models are non-linear mixed effect models (Van Der Graaf and Gabrielsson, 2009, Aarons et al., 2001). They combine structural (fixed) and stochastic (random) models to describe the disposition of drugs. The structure can be one (Ren et al., 2019), two (Karatza and Karalis, 2019), or multi compartments (Asaumi et al., 2019). The parameters in the structural model are known as fixed-effects, and are relevant for the characterization of the absorption (k_a and F), distribution (V), and elimination (CL or Q). The stochastic model accounts for the magnitude, and the sources of variability in the fixed-effect parameters. The parameters in the stochastic part are known as random-effect.

The two main types of random effects in population pharmacokinetic model are the inter-individual variability (IIV) and the residual error variability. The IIV describes differences between individuals which may be attributed to demographic, physiological and biochemical differences. The residual error model on the hand accounts for the error associated with the collection of the pharmacokinetic samples and potential misspecification of the structural PK model.

2.1.4 Schematic presentation of Population pharmacokinetic models

Theoretical or imaginary compartments are used to illustrate pharmacokinetic models in a simplified way. The organs and tissues of the body are represented by the compartments. The number of compartments in a model depends on the assumptions regarding the absorption, distribution and elimination of drug from the body. A population pharmacokinetic model may thus be described as one-compartment, two-compartment or multi-compartment model.

A one compartmental model assumes that the distribution of drug is limited to only a central compartment after administration. This central compartment represents all tissues that are able to achieve rapid equilibration with the plasma drug concentration. A two compartmental model on the other hand, has an additional peripheral compartment that achieves equilibration a little later. Thus, there is a flux of drug between the central and peripheral compartment as illustrated in **Figure 2**.

Figure 2. Schematic representation of one and two-compartmental models after IV and oral administration.

2.1.5 Exposure measures

The exposure of a drug describes its concentration in circulation or at the site of action over a defined period of time. It is important in pharmacokinetics to determine the exposure levels that are relevant to achieve a therapeutic response to a drug. The exposure measures commonly used to define the exposure levels are the Ctrough, Cmax, Tmax, Tmin, and AUC.

Ctrough is the minimum quantifiable concentration of a drug measured at time Tmin. Cmax, on the other hand, is the maximum concentration of a drug measured at time Tmax. The AUC is the concentration under the concentration-time curve calculated to determine the total concentration of a drug over a period of time. The AUC can be

estimated using non-compartmental analysis (NCA), whereas, the C_{trough} , T_{min} , C_{max} and T_{max} can be determined directly from the concentration-time data.

2.2 STATISTICAL CONCEPTS

2.2.1 Mathematical presentation of population pharmacokinetic models

The mixed effect model (Drikvandi, 2017) can be represented by the following equations:

$$y_{ij} = f(t_{ij}, \varphi_i, D) + \varepsilon_{ij}$$

$$\varphi_i = \varphi_{\text{pop}} + \eta_i$$

Where

$$\varepsilon_{ij} = \sim \text{iid } N(0, \sigma^2)$$

$$\eta_i = \sim N(0, \omega_i^2)$$

- $y_{i1}, \dots, y_{ij}$: j repeated measurements on the i th subject, where y_{ij} is the plasma concentration for subject i measured at time t_{ij} .
- f is a nonlinear function of time which depends on the φ and D . The function can be a one, two, or multi-compartmental model.
- D is the dose of drug administered
- φ_i are individual parameters
- φ_{pop} is a vector of population parameters
- ε_{ij} is the residual errors associated with plasma concentration measurements, y_{ij}

The nonlinear mixed effect model is the joint probability distribution of (y, φ) :

$$p(y, \varphi ; \theta) = \prod_{i=1}^N p(y_i, \varphi ; \theta)$$

$$p(y, \varphi ; \theta) = \prod_{i=1}^N p(y_i, \varphi ; \theta) * p(\varphi ; \theta)$$

2.2.2 The population pharmacokinetic model of melphalan

The pharmacokinetic profile of melphalan was described by two-compartmental model (**Figure 2**) and expressed by equations below:

The likelihood of melphalan parameters after a dose of D is infused at time T_{inf} is expressed as:

$$L(CL, V1, Q, V2, \sigma^2 | y_1, \dots, y_n, t_1, \dots, t_n, t, D) = \prod_{i=1}^n L(CL, V1, Q, V2, \sigma^2 | y_i, t_i, D)$$

$$= \frac{1}{\sqrt{2\pi\sigma}} * e^{-\frac{1}{2\sigma^2} * (y - \hat{y}(CL, V1, Q, V2, t, D))^2}$$

$$y(CL, V1, Q, V2, t, D) = A * e^{-\alpha t} + B * e^{-\beta t} \dots \dots \dots (1)$$

Where:

$$A = \frac{1}{V1} * \frac{k_{21} - \alpha}{\beta - \alpha}$$

$$B = \frac{1}{V1} * \frac{k_{21} - \beta}{\alpha - \beta}$$

$$\alpha = \frac{1}{2} * [k_{sum} - \sqrt{k_{sum} * k_{sum} - 4 * k_{21} * k_{10}}]$$

$$\beta = \frac{1}{2} * [k_{sum} + \sqrt{k_{sum} * k_{sum} - 4 * k_{21} * k_{10}}]$$

$$k_{10} = \frac{CL}{V_1}$$

$$k_{12} = \frac{Q}{V_1}$$

$$k_{21} = \frac{Q}{V_2}$$

$$k_{sum} = k_{10} + k_{12} + k_{21}$$

Hence given the pharmacokinetic parameters of melphalan, the plasma concentration (C) at time, t, after an intravenous infusion, D, administered at time, tD, over a period of Tinf can be given by the function below:

If $t - tD \leq T_{inf}$

$$C(t) = \frac{D}{T_{inf}} * \left[\frac{A}{\alpha} * (1 - e^{-\alpha * (t - tD)}) + \frac{B}{\beta} * (1 - e^{-\beta * (t - tD)}) \right] \dots \dots \dots (2a)$$

If not,

$$C(t) = \frac{D}{T_{inf}} * \left[\frac{A}{\alpha} * (1 - e^{-\alpha * T_{inf}}) * e^{-\alpha * (t - tD - T_{inf})} + \frac{B}{\beta} * (1 - e^{-\beta * T_{inf}}) * e^{-\beta * (t - tD - T_{inf})} \right] \dots \dots \dots (2b)$$

The function describing the two compartment or biphasic disposition of melphalan is presented by the differential equations below:

$$\frac{dA_1}{dt} = A_2 * k_{21} - A_1 * k_{12} - A_1 * k_{10} \dots \dots \dots (3)$$

$$\frac{dA_2}{dt} = A_1 * k_{12} - A_2 * k_{21} \dots \dots \dots (4)$$

2.2.3 The Bayes Rule

For Bayesian approaches, a prior is required for the computation of a posterior distribution in accordance with the Bayes Rule (**equation 5**). The Bayes rule is the basis for inference about the Bayesian population PK parameters (θ : CL, V1, Q and V2) given the data (y) and prior knowledge about model parameters ($p(\theta)$). The parameters are viewed as random variables with probability distributions that naturally permit the characterization of the uncertainty around them.

$$p(\theta|y) = \frac{p(\theta) * p(y|\theta)}{p(y)} \propto p(\theta) * p(y|\theta) \dots \dots \dots (5)$$

Where:

- $p(\theta|y)$ is the posterior distribution of the parameter given the data;
- $p(\theta)$ is the prior distribution of the parameters;
- $p(y|\theta)$ is the likelihood function expressed by **equation (1)**.

2.2.4 The Prior distribution

The prior in Bayesian statistics represents our prior beliefs or knowledge about a parameter. Priors can be informative, weakly informative or uninformative. Informative prior strongly represents information that prevents the data alone from influencing the posterior distribution. Uninformative prior on the other hand allows the data alone to influence the posterior distribution because it lacks information. Weakly

informative priors contain some information about the parameter, but allows the data to significantly influence the posterior distribution. In this work both informative priors, parameters from non-Bayesian estimation, and weakly informative priors were used.

Normal priors for the mean of CL, Q, V1, and V2 were used. Cauchy priors were used as weakly informative priors for the omega and sigma parameters. The LKJ priors were used on the *rho* parameters. The omega parameters are the variances (diagonals) of the variance-covariance matrix of the etas on CL, Q, V1 and V2, whereas the rho parameters are the off-diagonal covariance. The sigma parameters are the variances of the residual errors. The LKJ is the Cholesky LKJ correlation distribution, and is implemented in Stan to model a covariance matrix of a multivariate normal distribution (Sorensen and Vasishth, 2015).

2.2.5 The posterior distribution

The posterior distribution as shown in **equation (5)** summarizes our current state of knowledge about a parameter after prior information and data (likelihood) (Gelman, 2002). Hence with prior information about melphalan PK parameters, and plasma concentration data, we are able to generate the marginal distribution for each of the PK parameters; CL, Q, V1 and V2.

2.2.6 Posterior predictive distribution

New data (y_{new}) can be predicted from the posterior distribution using the posterior predictive distribution expressed by equation (6). The predicted data is then compared with the observed data to determine the accuracy and adequacy of the model.

$$p(y_{new}|y) = \int p(y_{new}|\theta) * p(\theta|y)d\theta \dots \dots \dots (6)$$

2.2.7 Estimation methods

Estimation methods are used to determine the parameters of a model. In frequentist Statistics, the maximum likelihood is one of the commonly used estimation methods. It finds a set of parameters that maximizes a likelihood function or minimizes the negative log-likelihood of that function. In population pharmacokinetics, the calculation of the likelihood is complex since the random effects have to be integrated out. To circumvent this difficulty, population pharmacokinetic modeling packages implement methods that approximate the true likelihood with another simplified function (Mould and Upton, 2013). Some of this approximation techniques include the first order-method (FO), and the first-order conditional estimation (FOCE) methods (Bauer, 2019). In this work, the non-Bayesian estimation was done in NONMEM using the FOCE method.

Bayesian techniques on the other hand are based on Markov Chain Monte Carlo (MCMC) simulation, which overcomes the complex integration processes involved in estimating population pharmacokinetic model parameters. Bayesian techniques

therefore do not approximate marginal distribution of the parameters, but gives a sample distribution of probable population parameters with mean similar to the maximum likelihood values (Bauer, 2019).

2.2.8 The Markov Chain Monte Carlo Simulation (MCMC)

Markov chain simulation or MCMC is based on sequential random sampling of parameter values from an approximate distributions, and the corrections applied to those draws help to better approximate the posterior distribution (Gelman et al., 2013). Any aspect of the posterior distribution may be approximated exactly with a large number of Monte Carlo samples (Hoff, 2009). To generate MCMC samples with minimal autocorrelation, one needs a large sample draw with the appropriate thinning parameter. Samples drawn during the warm-up phase, i.e. before the convergence of the Markov chains, are discarded.

2.2.9 Algorithms for MCMC

Algorithms used to implement MCMC include Gibbs sampling (GS), Metropolis-Hastings (MH), and the Hamiltonian Monte Carlo (HMC) simulation. Gibbs sampling generates draws for the posterior distribution by sampling from the univariate full conditional distributions.

$$\theta_1^i \sim p(\theta_1 | \theta_2^{i-1}, \theta_3^{i-1}, \dots \dots \theta_n^{i-1}, y)$$

$$\theta_2^i \sim p(\theta_2 | \theta_1^i, \theta_3^{i-1}, \dots \dots \theta_n^{i-1}, y)$$

$$\theta_n^i \sim p(\theta_n | \theta_1^i, \theta_2^i, \dots \dots \theta_{n-1}^i, y)$$

The Metropolis Hastings algorithm is a general multipurpose MCMC algorithm which requires a conditional proposal density which is easy to sample from. The HMC algorithm is sensitive to two important parameters, step size (ϵ), and the number of steps (L), which when properly tuned, avoids the random walk behavior and sensitivity to correlated parameters by taking a series of steps informed by first-order gradient information (Neal, 2011, Hoffman and Gelman, 2014). This allows the Markov chain to converge to high dimensional target distribution quicker than the Gibbs and Metropolis sampling (Hoffman and Gelman, 2014).

The NUTS (No-U-Turn Sampler) is an extension of the HMC algorithm. It eliminates the need to tune the number of steps (L). In effect, an empirical NUTS will perform as efficiently as a properly tuned HMC without requiring user tuning (Hoffman and Gelman, 2014). The NUTS algorithm has been implemented in Stan, and has been showing promise to estimating population pharmacokinetic and pharmacodynamic models. Examples can be found on the website of Metrum Institute® (<https://www.metrumrg.com/course/brief-introduction-bayesian-modeling-using-stan/>). In this work, Stan was used for the Bayesian part of the analysis.

2.2.10 Standard Normal Deviate and the Standard Normal Distribution

The standard normal deviate (SND) is derived from the normal distribution .

$$SND = \frac{(\mu - x)^2}{\sigma}$$

The normal distribution is a bell-shaped density curve, symmetrical about its mean (μ) with a spread determined by its standard deviation (σ).

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} * e^{-\frac{1}{2}*\left(\frac{x-\mu}{\sigma}\right)^2}$$

The density is called the standard normal distribution when its mean is zero (0) and standard deviation is one (1).

$$f(x) = \frac{1}{\sqrt{2\pi}} * e^{-\frac{1}{2}*x^2}$$

The standard normal distribution has wide application in science. It has been used in reporting analytical results and to guide decision making. For instance, data are standardized by subtracting the mean (x) from a reference (μ), and dividing this difference by the standard deviation (σ) to construct control charts (Amin, 2001). The control charts are then used to guide the acceptance and rejection of analytical or manufacturing batches.

CHAPTER 3

3 METHODOLOGY

3.1 Overview of methodology

The method used in this study is outlined in **Figure 3**. This included literature search for melphalan PK models, simulation of the published PK models, evaluation and selection of the PK models, creation of composite melphalan PK dataset, and the creation of melphalan composite PK model.

Figure 3. Outline for developing a composite pharmacokinetic model. mSND, modified standard normal deviate.

3.2 Literature search for melphalan PK models

Six papers describing 7 melphalan Pop PK models were selected for analyses from PubMed. These six papers (Nath et al., 2010, Nath et al., 2007, Mizuno et al., 2018, Kuhne et al., 2008, Cho et al., 2018, Mougenot et al., 2004, Cho et al., 2017) are the only available published articles that describe melphalan Pop PK. They have been summarized in **Table 1**. The EVOMELA PK reported in the Clinical Pharmacology NDA Review packet (Nov, 2015) was used as the reference model.

3.3 Design and Simulations

After selecting the melphalan models, each of them was simulated using their respective published pharmacokinetic parameters. The design of the simulation was the same for each model with respect to virtual subjects, covariate distribution, dose and mode of administration of melphalan. A total of 1000 virtual subjects were simulated. Primary covariates, i.e. the covariates that can be measured directly, were simulated using the normal distribution:

$$\text{Primary Covariate} \sim N(\mu, \sigma)$$

The mean (μ) and standard deviation (σ) used for simulating the covariates are presented in **Table 1**.

Table 1. Summary of demographic and study-related characteristics of literature used in this study.

Model	1 and 2	3	4	5	6	7
Reference	C E Nath et al 2010 (a/b)	C E Nath et al 2007	Mizuno et al 2018	Kuhne et al 2008	Cho et al 2017	Mougenot et al 2004
Demography						
Number of subjects	100	59	15	84	146	64
Gender (M/F)	59 / 41	38 /21	11-Apr	53 / 31	90 / 56	22 /42
Age (yrs)	36-73	0.3 - 18	48-74	37-77	35-72	19-80
Height (cm)	147-185	92 -137	-	155-188	-	152 - 185
BSA	1.3-2.6	0.60 - 1	1.5 – 2.51		-	1.37 – 2.21
Study Population						
Population characteristics	Multiple myeloma patients undergoing ASCT	Malignant disease children undergoing autologous and allogenic BMT	Multiple myeloma patients undergoing HSCT	Multiple myeloma, non-Hodgkin's lymphoma, rare tumors	Multiple myeloma patients admitted for HSCT	Advanced malignancies
Model Covariates						
BWT (kg)	42 – 132	13.5 – 28.1	51.2-134.8	48-130	-	35 - 102
FFM	34.4-80.5	-	-	-	31.3 – 81.9	-
HCT	20-45	-	-	-		-
CrCL (ml/min)	29-234	-	35 - 164	11.9 – 179.8		30 - 195
GFR(ml/min 1.73m ²)	-	86 - 139	-	-	-	-
Pharmacokinetics						
Fraction analyzed	Total/Unbound	Total	Total	Total	Total	Total
Dose:	IV	IV	IV	IV	IV	IV
Infusion rate	15-95 min	15 min	20 min	20-30 min	-	24 hr
Dose Range	192 mg/m ²	140 or 180 mg/m ²	140 or 180 mg/m ²	10-200 mg/m ²	140 or 200 mg/m ²	20 to 30 mg/m ²
Structure of PK model	2CMT	2CMT	2CMT	2CMT	2CMT	2CMT

Table 2. List of covariates used in the simulations.

Variable	Unit	Mean	Standard deviation
Weight (WT)	Kg	70	14
Age	years	60	12
Height (HT)	cm	170	34
Serum Creatinine (SCR)	mg/dl	1.1	0.22
Hematocrit (HCT)	%	34	6.8

The derived covariates were calculated from the primary covariates using the equations below:

$$BMI = \frac{WT}{(HT_{in\ cm}/100)^2}$$

$$BSA = 0.024265 * HT^{0.3964} * WT^{0.5378}$$

$$CrCl_{Male} = \frac{(140 - AGE) * WT}{(72 * SCR)}$$

$$CrCl_{Female} = \frac{0.85 * (140 - AGE) * WT}{(72 * SCR)}$$

$$FFM_{Male} = \frac{9.27 * 1000 * WT}{6.68 * 1000 + 216 * BMI}$$

$$FFM_{Female} = \frac{9.27 * 1000 * WT}{8.78 * 1000 + 244 * BMI}$$

The proportion of female to male virtual subjects was 2:3. Using a 30 minutes IV infusion of 140 mg/m², each model was simulated using the respective published pharmacokinetic parameters.

3.3.1 Calculation of Exposure measures

The exposure measures, AUCinf and Cmax, were determined using NCA implemented in PKNCA R package. The AUC was estimated using the trapezoidal rule (Gabrielsson and Weiner, 2012) and the Cmax corresponded with the highest concentration after IV infusion.

3.3.2 Calculation of the modified standard normal deviates (mSND)

The standard normal variate was calculated as follows:

1. Compute the average of each exposure measure.

$$\mu_{\text{AUCinf}} = \frac{\text{AUCinf}_1 + \text{AUCinf}_2 + \dots + \text{AUCinf}_n}{n}$$

$$\mu_{\text{Cmax}} = \frac{\text{Cmax}_1 + \text{Cmax}_2 + \dots + \text{Cmax}_n}{n}$$

2. Compute the standard deviation of each exposure measure.

$$\sigma_{\text{AUCinf}} = \sqrt{\frac{\sum_{i=1}^n (\text{AUCinf}_i - \mu_{\text{AUCinf}})^2}{n - 1}}$$

$$\sigma_{C_{\max}} = \sqrt{\frac{\sum_{i=1}^n (C_{\max_i} - \mu_{C_{\max}})^2}{n - 1}}$$

3. Compute the modified standard normal deviate of each i th model.

$$AUC\ SND_i = \frac{(\mu_{AUC_{inf}} - AUC_{inf_i})^2}{\sigma_{AUC_{inf}}}$$

$$C_{\max}\ SND_i = \frac{(\mu_{C_{\max}} - C_{\max_i})^2}{\sigma_{C_{\max}}}$$

4. Plot each of the models for a visual presentation of their deviates **Figure 1**.

3.4 Selection of melphalan pharmacokinetic models

A criterion of 0 – 3 mSND was used for model selection based on its ability to discriminate between models which were developed using different PK data and different model structure. The models within 0 -3 mSND were selected for repurposing, and subsequently used to generate a composite dataset for the development of the composite PK model.

3.5 Development of the Composite Pharmacokinetic Model

3.5.1 Non-Bayesian approach (FOCE-I)

The composite dataset was used to develop a composite PK model. The composite dataset consisted of 100 virtual subjects. A two compartmental pharmacokinetic model was developed in NONMEM using First-order conditional estimation method (FOCE) with interaction. FOCE-I is an approximation of the maximum likelihood estimation method. The parameters estimated included CL, Q, V1 and V2. Inter-individual variability (IIV) or η associated with each of the parameters were estimated. The residual error variability or sigma (σ) was also estimated. The final model was evaluated using the goodness of fit (GoF) plots (dataset versus predictions, and residuals).

3.5.2 Bayesian Method

The Bayesian methodology was implemented in Stan using the NUTS MCMC algorithm to develop a two compartmental model. The model is expressed by **equations (2a & b)**. Both weakly informative priors and informative priors of the fixed effects, CL, Q, V1, and V2 were examined during runs 1 and 2 respectively (Table 3). All other priors were weakly informative.

Table 3. Priors used for the Bayesian model development.

Parameter	Run 1	Run 2
CL	normal(0, 25)	normal(27.7, 25)
Q	normal(0, 50)	normal(19, 50)
V1	normal(0, 10)	normal(27.4, 10)
V2	normal(0, 20)	normal(15.7, 20)
omega	cauchy(0, 1)	cauchy(0, 1)
rho	*lkj_corr(1)	lkj_corr(1)
sigma	cauchy(0, 1)	cauchy(0, 1)

The posterior distribution were expressed as:

$$\text{Log}(\varphi) \sim \text{multi_normal}(\text{log}(\varphi), \text{Omega})$$

$$C \sim \text{lognormal}(\text{log}(y(\text{CL}, \text{V1}, \text{Q}, \text{V2}, t, D)), \text{sigma})$$

The conditions for each run were: number of chains = 4; burn-in samples = 500, post-burn-in samples = 1000; number of iterations = 1500; and thinning number= 1.

The convergence of the Markov chains were assessed by examining the traceplots for stationarity and mixing of the four chains. A straight horizontal fuzzy caterpillar, rather than a wiggly snake, is an indication of adequate mixing and hence convergence. Also the potential scale reduction statistics (Rhat) was examined. The Rhat compares the between and within variances of the chains (Brooks and Gelman, 1998). An Rhat of 1 is an indication that all chains were in equilibrium and converged to a common distribution. Similar to the non-Bayesian approach, the composite dataset was compared with predictions from the model to evaluate the adequacy of the predictions.

CHAPTER 4

4 FINDINGS

4.1 Description of published melphalan Pharmacokinetic models

From the 6 published papers, 7 Pop PK models of melphalan were selected, and simulated (**Figure 4**). The 7 models represented melphalan PK in about 450 patients with multiple myeloma (MM) and malignancies, who were undergoing allogenic or autologous stem cell transplantation.

Figure 4. Individual plots of simulated plasma concentration of melphalan: after 30 minutes IV infusion of 140 mg/m^2 of melphalan. M1: Nath et al. 2010a ; M2: Nath et al. 2010b; M3: Nath et al. 2007; M4: Cho et al. 2018; M5: Kuhne et al. 2007; M6: Mizuno et al. 2018; M7: Mougenot et al. 2004.

Melphalan doses of 20 – 200 mg/m² were administered in the original studies (**Table 1**). The data used to develop the original published models were from total melphalan plasma concentration, except M2 (Nath et al., 2010), which was developed using unbound concentration. Additionally, the original studies were conducted in adult patients except M3 (Nath et al., 2007), which was conducted in pediatric patients.

The PK models were all described as two compartment models except M7 (Mougenot et al., 2004), which was described as a one-compartmental model. At least, body weight or other measures of body weight was used as a covariate on a parameter in all the models used in this study. Other covariates found included creatinine clearance (CrCl), glomerular filtration rate (GFR), and hematocrit (HCT).

4.2 The modified standard normal deviate (mSND) provided a criterion for discriminating published melphalan PK models.

The modified standard normal deviate (mSND) used in this work provided an approach for discriminating the predictive performance of the published PK models. Models with exposure measures within a mSND of 0-3 were considered to be predictive of the 140 mg/m² melphalan dose. Predictions of AUC_{inf} and C_{max} were all within 0-3 SND, except M2 (*Nath et al. 2010b*) and M7 (*Mougenot et al. 2004*) which deviated by more than 3 units (**Table 4 & Figure 5**). This suggests three important things regarding the published melphalan Pop PK models.

Table 4. Summary of the modified standard normal deviates (mSND) of 7 published melphalan PK models.

Model Number	Published Paper	C _{max} (mg/L)	SND of C _{max}	AUC (mg.hr/L)	SND of AUC
M1	Nath et al. 2010a	9.1	2.2	9.4	2.9
M2	Nath et al. 2010b	1.9	8.4	2.0	6.5
M3	Nath et al. 2007	9.5	2.9	8.6	1.5
M4	Cho et al. 2017	7.6	0.3	8.7	1.6
M5	Kuhne et al. 2007	7.1	0.1	7.2	0.2
M6	Mizuno et al. 2018	7.4	0.2	6.8	0.0
M7	Mougenot et al. 2004	4.1	2.4	2.6	5.1

Firstly, it suggests that the data used to generate melphalan PK model is an important factor that can limit future predictions. Models based on unbound melphalan plasma concentration may not predict total plasma concentration adequately without an appropriate correction factor. For this reason, caution should be exercised when such models are repurposed to predict total plasma concentrations.

Second, the structure of the Pop PK model is a source of variability in predictions. This is consistent with the higher mSND associated with the AUC_{inf} predicted by M7 (*Mougenot et al. 2004*) presented in **Figure 5**. In the study design of M7 (*Mougenot et al. 2004*), unlike the other papers, melphalan was infused for more than 24 hours. M7 design informed a one compartment model structure, and was inadequate to predict melphalan PK after short IV infusion like the others.

Lastly, irrespective of the covariate used to explain between-subject variability in PK, majority of the models predicted AUC_{inf} and C_{max} within 3 mSND. This suggests that any of those models within 0-3 mSND; M1, M3, M4, M5, and M6; could be selected

and repurposed based on the covariates one can afford to measure. Alternatively, a composite model which combines all the eligible models can be developed and repurposed rather than selecting one.

Figure 5. The modified standard normal deviates (*mSND*) based on *AUC* and *Cmax*.

4.3 A 2-compartmental model adequately fit the melphalan composite data using FOCE-I.

Using the non-Bayesian approach, a two compartmental model was developed from composite data generated from models M1, M3, M4, M5, and M6. The goodness of fit plots (GoF) showed adequate fit of the two compartmental model to the composite data (**Figure 6**). The model parameters were: clearance (CL), 27.7 L/hr; distributional clearance (Q), 27.4 L/hr; volume of central compartment (V1), 19 L; and volume of peripheral compartment (V2).

Figure 6. Goodness of fit plot of the composite PK model using FOCE-I.

Table 5. Pharmacokinetic parameters of the composite melphalan PK model using Bayesian HMC-NUTS estimation.

Parameters based on weakly informative priors						
	Mean	SD	2.50%	97.50%	n_eff	Rhat
CL	27.72	1.12	25.60	30.08	1836	1.00
Q	25.57	2.44	20.89	30.56	14	1.08
V1	19.08	1.03	17.13	21.17	1383	1.01
V2	15.65	1.03	13.67	17.68	1124	1.01
sigma	0.005	0.0001	0.005	0.005	1402	1.00
omega[1]	0.41	0.03	0.36	0.47	1646	1.00
omega[2]	0.87	0.13	0.64	1.12	3	1.65
omega[3]	0.55	0.04	0.48	0.64	61	1.03
omega[4]	0.62	0.05	0.53	0.73	32	1.04
Parameters based on informative priors						
	Mean	SD	2.50%	97.50%	n_eff	Rhat
CL	27.95	1.16	25.79	30.28	3821	1.00
Q	25.94	2.45	21.10	30.82	16	1.07
V1	19.42	1.08	17.36	21.63	2672	1.01
V2	15.75	1.04	13.82	17.85	2852	1.01
sigma	0.005	0.0001	0.005	0.005	3809	1.00
omega[1]	0.41	0.03	0.36	0.47	4376	1.00
omega[2]	0.87	0.13	0.65	1.11	3	1.65
omega[3]	0.55	0.04	0.48	0.64	70	1.02
omega[4]	0.62	0.05	0.53	0.72	47	1.03

4.4 A 2-compartmental model adequately fit the melphalan composite data using HMC – NUTS MCMC.

Again, a two-compartmental model adequately fit the composite data when Hamiltonian Monte Carlo No-U-Turn-Sampler MCMC was used. This Bayesian methodology confirmed the non-Bayesian model developed using FOCE-I. Both informative and weakly-informative priors gave similar parameter estimates (**Table 5**). The traceplots and Rhat presented in the **Appendix** indicated successful convergence and adequate mixing of the chain.

Table 6. Comparison of pharmacokinetic parameters of composite and reference (Evomela NDA) melphalan models.

Parameter	Reference	FOCE-I	NUTS-MCMC	
			Weakly Informative Prior	Informative Prior
CL (L/hr)	27.07	27.7	27.72	27.95
Q (L/hr)	23.22	27.4	25.57	25.94
V1 (L)	20.29	19	19.08	19.42
V2 (L)	14.61	15.7	15.65	15.75
Omega 1 (%)	-	40.6	41	41
Omega 2 (%)	-	60.5	87	87
Omega 3 (%)	-	55.3	55	55
Omega 4 (%)	-	63.9	62	62
Sigma (mg/L)	0.036	0.0132	0.005	0.005

FOCE-I, First-order conditional estimation with interaction; CL and Q are clearance parameters, V1 and V2 are volume of distribution parameters; Omega 1, 2, 3 and 4 are the etas (inter-individual variability parameter) on CL, Q, V1 and V2 respectively.

4.5 The Bayesian and non-Bayesian composite PK models of melphalan agree with the reference EVOMELA NDA model

The reference model from the EVOMELA NDA packet was compared with the composite models developed using both Bayesian and non-Bayesian approaches. The parameter estimates (**Table 6**) and the model predictions (**Figure 7**) agree with those from the EVOMELA NDA packet. This confirmed that the modified standard normal deviate was able to select models with similar predictive performance, and those models could be combined into a composite model. Again, the agreement between the composite model and the reference suggests that literature data can be repurposed to develop composite PK models.

Figure 7. Comparison of predictions from melphalan composite models and reference (EVOMELA NDA) model. The predictions of the composite and reference models are in agreement with each other. EVOMELA NDA; Reference model; FOCE-I First-order conditional estimation with interaction; NUTS:InPr, Bayesian composite model with informative prior; NUTS:WkInPr, Bayesian composite model with weakly informative prior. Shaded region is 95% confidence interval of EVOMEL NDA model.

4.6 Potential areas of application and summary of findings

Model and parameter repurposing is common in quantitative clinical pharmacology, especially, in the development of complex quantitative systems pharmacology (QSP), and PBPK models. Usually, the base model and parameters are selected from literature and modified to provide evidence to support dosing and design of clinical trials. An example is the development of an integrated PBPK model of calcium homeostasis and bone biology (Peterson and Riggs, 2010), where three previously published models (Raposo et al., 2002, Lemaire et al., 2004, Bellido et al., 2003) served as the foundation for the new one. The new model with calcium homeostasis component (Peterson and Riggs, 2010) was then used to perform simulations to support the adequacy of proposed dosing regimen in regulatory review of *Natpara* in hypothyroidism (Khurana et al., 2019).

Similar to systems model, pharmacokinetic models of drugs may also be selected from literature and repurposed. Marketed drugs may have several PK models available in literature, which may be selected and repurposed to support the development of combination therapeutic products.

In this work, our approach offered two options for repurposing melphalan PK models (**Figure 8**). First, it offered us the option of choosing any of M1, M3, M4, M5, M6 or the reference model, depending on which covariates we are able to afford. Second, it offered us a composite model which averaged M1, M3, M4, M5 and M6, and may be used when we have no interest in covariates.

Figure 8. Models to choose from for repurposing. M1: Nath et al. 2010a; M3: Nath et al. 2007; M4: Cho et al. 2018; M5: Kuhne et al. 2007; M6: Mizuno et al. 2018; BWT, body weight; FFM, free fat mass; HCT, hematocrit; CRCL, creatinine clearance; GFR, glomerular filtration rate.

CHAPTER 5

5 CONCLUSION

The modified standard normal deviate provided an objective criterion for selection of melphalan models based on the prediction of exposure after a given dose. The approach showed that the PK data, unbound or total concentration, and model structure were sources of variability in the predictions of exposure measures.

Additionally, this approach guided the development of a composite Pop PK model which approximately averaged previous models. Bayesian, using informative and weakly informative priors, gave similar parameters and predictions like the non-Bayesian approach. Predictions from the composted models agreed with predictions from reference model in EVOMELA Clinical Pharmacology NDA Review packet. This confirms the validity of the composite model and the approach used.

It is hoped that further refinement of this approach will provide a more objective approach for selecting PK models for repurposing. In the future, the sample size for the SISA step can be optimized to mimic the proportion of subjects in the original studies. Additionally, the uncertainty associated with each parameter may also be evaluated

6 APPENDICES

6.1 Bayesian Diagnostics: pair plots (using informative priors)

6.2 Bayesian Diagnostics: pair plots (using weakly informative priors)

6.3 Bayesian diagnostics: traceplots (left: informative priors; right weakly informative priors)

6.4 Bayesian: Parameter distribution

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