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Process of Modeling Pharmacokinetics Using Nonlinear Mixed-Effect Models

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1. Abstract

Important to the world of pharmacology and drug discovery is the process of pharmacokinetic modeling. This part of the process gives developers and clinicians a basis of knowledge on how a drug moves through the body. This project focuses on three types of models: non-compartmental analysis, nonlinear mixed-effects models, and physiologically-based pharmacokinetic models. Each model differs in complexity and varies in the information it can provide. With an understanding of each type of model and an overview of the functions each serves, two drugs are examined in this project. The data collectors working on each project identified the level of modeling, i.e. the types of models they wanted for their drug.

The first is a drug called Tulathromycin. The data collectors on this project requested non-compartmental analysis. This individual project served largely as an introduction to the process of modeling and the programs that were required at each step. Following Tulathromycin, a second project was completed with a drug called Flunixin Meglumine. It was requested that nonlinear mixed-effects models be created for this drug. This second project expounded upon the knowledge gained in the Tulathromycin project, and went further to create a more complex model that gave the data collectors more freedom and knowledge about how the drug could be applied. The process of selecting a model and the criteria used by the programs for selection is reported and discussed in the section for Flunixin Meglumine.

Finally, this overall project examined a real-life application of pharmacokinetic models in order to provide perspective of their use. Neither model that was worked with hands-on used the observations for predictive models, so it is central that a common application like this was examined. Overall, models like these are central in allowing clinical observations to pave the way for knowledgeable dosing regimens in animals. These models are used by clinicians to predict the recommended administration amount and method, and allow them to take in covariates of the subject they are working with. The predictive knowledge informs confident and safe dosing strategies in the world of medicine and pharmacology.

2. Introduction

Pharmacokinetic models have a multitude of applicative uses, and they are often a fundamental part of clinical trials. They can be used to inform dosing strategies, enhance multi-drug administration, and identify covariates of an animal that may affect how it responds to a drug. While there are also various types of pharmacokinetic models, each method has its importance in giving desired information on a drug. Thus, modeling techniques can be chosen by identifying the simplest model that is able to give the requested information. Three models were discussed throughout the course of this project, and the brief analysis of each to follow gives insight as to which model is best for the desired outcome.

One of the simplest models to describe the pharmacokinetics of a drug is non-compartmental analysis. With data that has information on the concentration of the drug in the body over time for each individual in the study; this type of model works to explain the drug in its simplicity, that is, how it is being absorbed, how it is being eliminated, and the total amount of the drug that makes its way into and out of the body. Figure 1, to the left, shows a typical drug concentration curve. In performing non-compartmental analysis, programs are analyzing the different phases of the graph to obtain parameters. The first phase is the absorption phase, characterized by an increase of the drug in the body. This is due to the fact that the absorption rate multiplied by the amount of drug available for absorption is larger than the elimination rate multiplied by the amount of drug in the body (Jambhekar & Breen, 2012). These values reach an equilibrium, and then the elimination phase of the curve is observed. In contrast to the absorption phase, the elimination phase is characterized by the value of the elimination rate multiplied by the amount of drug in the body being larger than the value of the absorption rate multiplied by the amount of drug available for absorption (Jambhekar & Breen, 2012). Using these phases, and changes in the curve over time, the program is able to give parameters that describe the pharmacokinetics of the drug.

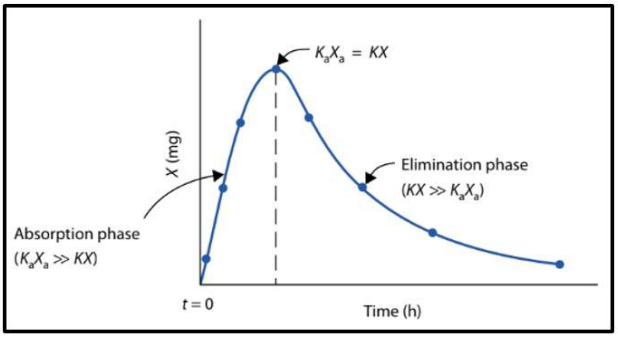

Fig 1. A typical drug concentration curve showing the amount of drug (X) in the body over time. K and K_a, elimination rate and absorption rate constants, respectively; X_a, amount of drug available for absorption. (Jambhekar & Breen, 2012).

The second model gives greater insight as to how the drug is moving within the body, and details from nonlinear mixed-effects (NLME) models can be used to extrapolate the collected data to situations that have not yet been tested. These models not only seek to explain the same parameters as the non-compartmental analysis, but also aim to describe how the drug is moving within the individual after being absorbed and before being excreted. Similar to non-compartmental analysis, NLME models require repeated measurements of a response, and often this is in the form of concentration measurements taken over time. These types of models split the body into compartments, and use ordinary differential equations (ODEs) to describe how these drugs move between the compartments (Davidian, 2004). These ODEs are informed by the parameters estimated by the program being used to create the models (Davidian, 2004). After creating an accurate model, these parameter estimates and mathematical equations can be used for predictive studies of tests that have not yet been performed (Davidian, 2004).

The final model discussed in this project was not worked with directly, and thus, will only be explained briefly. These models are called physiologically-based pharmacokinetic (PBPK) models. They have applications in attempting to explain why a drug behaves within the body the way it does. PBPK models take into consideration the physiological pathways in the body that are directly influenced by the drug (Sun et al., 2020). In this way, understanding how the physiology of the body behaves normally, and how it responds to covariates like illness, age weight, etc., come together to model how the drug behaves in the body under normal conditions and how it changes when these conditions are altered (Sun et al., 2020). Put simply, they are

beneficial because they work to explain the pharmacokinetics of a drug rather than merely modeling the observed effects or predicting outcomes based on the observed effects.

The two drugs directly examined in this project are Tulathromycin and Flunixin Meglumine. The first part of the project centered around Tulathromycin. This is an antibiotic used to treat respiratory bacterial pathogens (Clothier, 2010). The second part of the project, and the more extensive part, focused on Flunixin Meglumine. Flunixin Meglumine is a non-steroidal anti-inflammatory drug used in veterinary medicine, often for the treatment of pain and inflammation (Huber et al., 2013). While both projects centered around modeling the drugs, there were separate goals for each. Completing a non-compartmental analysis was the goal for Tulathromycin, and creating a NLME model was the goal for Flunixin Meglumine. The methods section to follow examines the process for each drug.

3. Methods

The pharmacokinetic modeling of both projects took on a framework of three phases; in order, the phases were data exploration, non-compartmental analysis, and nonlinear mixed-effects modeling. Each phase of the modeling process served an essential purpose to aid in further steps. Below, the phases of pharmacokinetic modeling are discussed in further detail, and then applied to separate modeling projects relating to the aforementioned drugs.

Data exploration was the first phase of modeling because it gave the modeler the opportunity to become familiar with the data and work it into a usable format. R Studio was the data exploration software used for the two separate projects. It is a statistical modeling software that allows for modification and early visualization of data. In both cases, the data received for the project was not presented in an acceptable format for the programs used later in the modeling process. Thus, coding in R Studio largely consisted of steps to correct inconsistencies in the data entry, and to modify the data so that each subsequent program had the information needed to perform the required analysis. Once the data was in an acceptable form for moving forward, the final step was to graph the data in R Studio, stratifying by individual, to get an initial look at the drug concentration graphs. This served to identify any outliers in the data and to make sure the concentration curves were presenting in a way that made sense for the movement of a drug within the body.

Following the data exploration phase, non-compartmental analysis was another partial phase of data exploration, but additionally served to give initial estimates of parameters that would be used later in the process of building a pharmacokinetic model. The program PKanalix, a product made by Lixoft, was used for this part of the project. Once the data was uploaded into the program, non-compartmental analysis was performed to give further information about the drug. For non-compartmental analysis, the program works to calculate the slope of the terminal elimination phase. This is represented by the variable λ_z, and if this value can be calculated, the program can calculate and report non-compartmental analysis parameters that are extrapolated to infinity (*PKanalix documentation*, n.d.). These parameters are useful in the next phase of creating a pharmacokinetic model.

The final phase of pharmacokinetic modeling is the phase consisting of building a representative model of the data. The models used in this project were nonlinear-mixed effects models, which were built in a program called Monolix, another program made by Lixoft. This phase of the project used initial parameters estimated by the previous phase to build a model to best fit the data. The models that are built into the program center around three different types: one compartment, two compartment, and three compartment models. These models are nested, that is, each subsequent model draws information from the previous. The one compartment model has a central compartment, the two compartment model has a central compartment with an additional peripheral compartment, and the three compartment model has a central compartment and two peripheral compartments. Monolix gives a likelihood associated with each model to describe the fit, and this parameter is partially informed by the Bayesian information criterion (*Monolix documentation*, n.d.). This is a mathematical process that focuses on choosing the lowest dimensional model while still capturing the data presented. In this way, regardless of increased information, this criterion still picks the lowest dimensional model to fit the data (*The Bayes Information Criterion*, n.d.). Once the best-fit model is identified, Monolix gives the option to explore various interfaces that give information about how well the selected model fits the data, and also allows for the analysis of covariates and their influence on the parameters of the model.

3.1. Tulathromycin

The outline given above was applied to two drugs in this project. The first was a drug called Tulathromycin. The goal of this project was to perform non-compartmental analysis on this drug, and it served largely as a learning tool of the programs that were mentioned above. The data set was a measurement of five tissue concentrations taken with respect to time in ewes. The data presented initially was not in a readable form for the programs, so the data exploration phase consisted mainly of learning the coding in R Studio to modify the data into a comprehensible form. One of the largest components of this phase was learning how to add an amount column to the data based on the information of dosing that was given. Once this was achieved, the data was graphed in R Studio, and stratified by the individuals, in order to allow for an initial look at the concentration curves with respect to time. These graphs were examined, and any identifiable outliers were addressed or removed.

From this point, the Tulathromycin project was fit for analysis in PKanalix. Uploading the data into the program gave a second look at the data which served as a brief, additional data exploration phase. After deeming all of the graphs fit for further analysis, the non-compartmental analysis was run through the program. The largest step of this phase was allowing the program to estimate the slope of the terminal elimination phase, as mentioned above, which allowed for the extrapolation estimates of parameters. At this point in the project, the analysis for Tulathromycin was complete with respect to what the data collectors had requested.

3.2. Flunixin Meglumine

After working with Tulathromycin and learning many of the skills required for pharmacokinetic modeling, a larger project that covered all three of phases of modeling was presented. This project centered around the drug Flunixin Meglumine (FM). The goal of this modeling project was to use nonlinear mixed-effects models to create an accurate pharmacokinetic model for the drug. This drug followed similar steps as the project above. The first goal was to complete the data exploration phase. Data for this project had been collected from three different people, all with various methods of data entry. Thus, the data exploration phase consisted largely of remedying the different data entry inconsistencies, and then combining the three separate data reports into one readable table for the programs to follow. When the data was acceptably formatted, the concentration versus time plots were created for each individual to give an initial look and ensure the curves made sense with what was expected for a pharmacokinetic concentration curve over time. At this stage in the process, the data was ready for non-compartmental analysis.

The goal of the FM project, unlike the Tulathromycin project, was to create a nonlinear mixed-effects model. Therefore, not only did the analysis in PKanalix serve as a secondary data exploration, but the parameter estimates were then also used in the actual making of a pharmacokinetic model. PKanalix was able to estimate the slope of the terminal elimination phase, and then report the necessary parameters for the initial estimates for the model. Once these were obtained, the data was uploaded into Monolix, where it underwent the initial stages of finding a suitable model. Three candidate models were made for the data: a one compartment model, a two compartment model, and a three compartment model. Each was a base-model for the data, and the next step of model building would require the identification of the best model out of the three, and then further modification of this model to better fit it to the data. At this time in the project, a meeting was held with the data collectors in order to provide an update on the status of the FM project, and to give a few initial parameter estimates that were obtained from the non-compartmental analysis. During this meeting, it was discovered that a few inconsistencies in the data had been overlooked originally, and needed to be re-addressed. Most notably, there were inconsistencies used in data entry relating to the dose and dosage columns, and there was a discontinuity with the way different data collectors entered the values for covariates of the animals. These inconsistencies needed to be rectified in order to move forward with the model building.

The project began back where it had left off at the data exploration phase after these problems were identified. Once these various discontinuities were addressed within the data, it was again uploaded to PKanalix for the calculation of the slope of the terminal elimination phase, and again the program gave initial parameter estimates. Moving forward to making model candidates, it was ultimately identified that a two compartment model had the highest likelihood. A schematic of the two compartment model can be found in Figure 2, right. This candidate was chosen to move forward for further modification in order to make a more accurate model. Various goodness-of-fit diagnostic plots are included in the results section below to demonstrate the models correlation with the observed data.

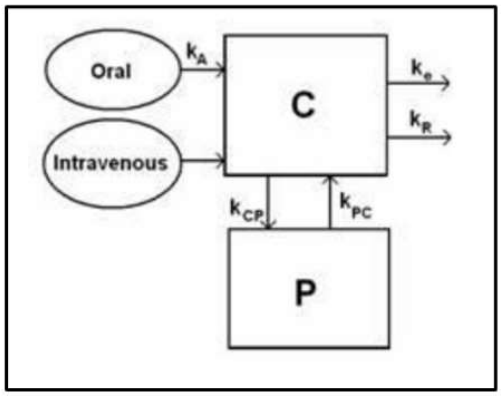

Fig 2. A general schematic for a two compartment nonlinear mixed-effects model. k_a and k_e, absorption and elimination parameters respectively. k_{CP} and k_{PC}, parameters describing the movement between the central and peripheral compartments, and describing the movement between the peripheral and central compartments, respectively. (Fogler & Gurmen, 2007).

4. Results

4.1 Tulathromycin

In PKanalix, the slope of the terminal elimination phase was successful for Tulathromycin. Thus, λ_z was extrapolated to infinity and the program was able to report parameter estimates; these values can be found in Table 1, right. Additionally, these parameter estimates gave information on making lines of best fit for each individual. A sampling of the individual plots with the lines of best fit are given in Figure 3, below. While there were parameter estimates that could be reported, after further examination of the data was ultimately not as useful as hoped. The parameters were still reported back to the data collectors along with a cautionary message about the viability of the data.

Table 1. Parameter estimate report. The mean area under the curve (AUC), clearance (Cl), maximum concentration (C_{max}), and slope of terminal elimination (lambda z) reported with the standard deviation and respective unit measurement.

Parameter	Units	Mean	Standard Deviation
AUC	Relative concentration-hours	11862.98	5430.29
Cl	Relative volume/hour	10.46	4.36
Cmax	Relative concentration max	322.83	123.35
Lambda z	1/hour	0.00375	0.00423

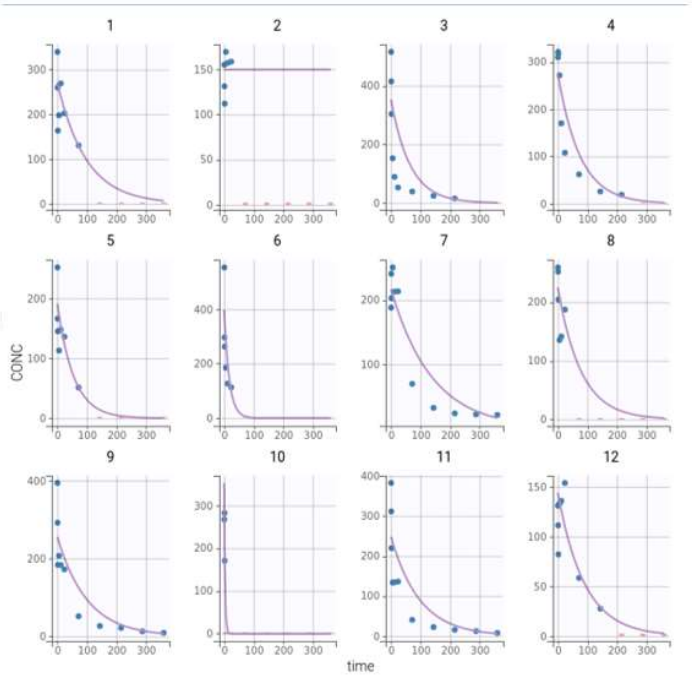

Fig 3. Individual plots of time-concentration curves with line of best fit superimposed on the observed data.

4.2 Flunixin Meglumine

Flunixin Meglumine, along with reporting parameter estimates from the NLME, were examined for goodness-of-fit to describe the level of accuracy of the predictive model. The parameter estimates can be found in Table 2 below.

Table 2. Parameter estimate report. Parameters reported with the residual squared error (RSE), standard deviation, and respective unit measurements.

Parameter	Unit	Estimate	RSE (error %)	Standard Deviation
Clearance	L/h	2.58	3.38	0.121
IV Absorption	1/h	78.8	14.3	1.64
Central Compartment Volume	L	3.36	6.09	0.183
Peripheral Compartment Volume	L	13.2	5.99	0.17

The parameter estimates given in Table 2 are the same parameter estimates given from the non-compartmental analysis for Tulathromycin; however, because FM was best modeled with a two compartment model, unlike Tulathromycin, it has two reported volume concentrations.

To examine how well this two compartment model fit the data, two separate goodness-of-fit tests were examined. The first test consisted of graphs, stratified by individual, that showed a visual representation of how well the population parameters matched the observed data for the individuals (*Monolix documentation*, n.d.). Figure 3 shows a group of twelve individual fits. It can be seen that in most of the individuals in the figure, both the curve of best fit and the population fit on the individual parameters have similarities in shape and are sometimes overlapping. There are three individuals in the figure, namely 147#5, 157#5, and 163#5, that appear to have disparities between the lines shown in the individual fit plots.

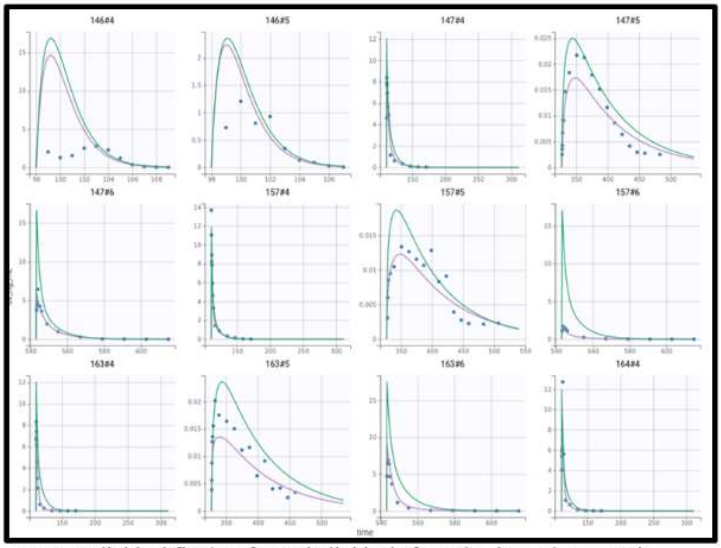

Fig 4. Individual fit plots for 12 individuals from the data. Plots contain observed data points, lines of best fit (purple), and population fits on individual parameters (green).

The second goodness-of-fit test was a graphical depiction of the residuals, shown in Figure 4. The residuals were measured in two different ways. The population weighted residual (PWRES) graph consists of residuals measured by comparing the observed data and the estimated population parameters. The individual weighted residual (IWRES) graph consists of residuals measured by comparing the observed data and the estimated individual parameters (*Monolix documentation*, n.d.). As expected, there is a larger variation for residuals of the PWRES graph versus the IWRES graph. Overall, the condensed plots, showing a small number of outliers, indicate that the model was fitted well to the observed data.

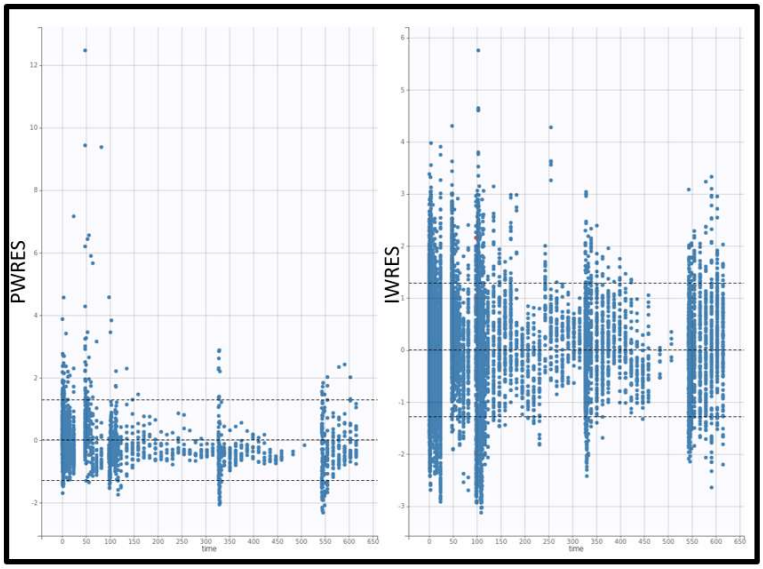

Fig 5. Scatter plots of the population weighted residuals (PWRES) and individual weighted residuals (IWRES) plotted with respect to time.

Although the goodness-of-fit tests completed for the NLME model for FM show a large degree of accuracy, this project did not extend to predictive models of the drug's actions in other scenarios. Because of this, a brief explanation of the real-life applications of these models was explored in a report that discussed the use of PBPK models in testing for drug interactions during coadministration. This study focused on olanzapine, an antipsychotic drug used for the treatment of schizophrenia. This drug often comes with an undesirable side effect of weight gain, so it is a good candidate for combining an alternative therapy to counteract the side effect. Samidorphan, an opiate, has the potential to restrain weight gain accompanying the administration of olanzapine (Sun et al., 2020). This study aimed at making a model for the coadministration of olanzapine and samidorphan. Researchers created separate PBPK models for each drug and their physiological profile based on observations from studies already completed. When accurate model candidates were created, researchers combined the PBPK models into a single model that focused on the coadministration of olanzapine and samidorphan (Sun et al., 2020). Using this model, they completed 10 virtual trials of 24 healthy subjects to examine the physiological interaction of the two drugs. They later examined adverse habits, like smoking, that had the potential to influence the associated physiological pathways and influence the drug interactions. In the end, this study found there to be no pharmacokinetic interaction between the two drugs (Sun et al., 2020). However, these PBPK models give a first hand look at the way they can change the process of drug design and reduce the cost and length of the drug discovery process; by using the correct tools, other models, too, have the potential to influence pharmacology in this way.

Common between all of these projects are the models and the information they are conveying. The method discussed first, non-compartmental analysis, is often good for an initial examination of a drug profile. It also serves to give early parameter estimates that in and of themselves are useful for early drug discovery and information, but also serve to inform later models if desired. The second type of models, nonlinear mixed-effect models, build upon non-compartmental analysis to form a wholistic picture of the pharmacokinetics of a drug. Not only can they describe more in-depth parameters like how the drug is moving between compartments in the body, but it can also take the estimated parameters to create predictive models for drug administration. The value of predictive models comes in describing outcomes that have not yet been tested. In this way, they can save time and costs that would normally needed to be spent on large-scale clinical trials and focus on predicting these virtually. Similar to the predicitive sense of nonlinear mixed-effect models, PBPK models can predict how drugs will behave in the body. In addition, PBPK models can serve to explain why a certain behavior is seen. These models focus on the underlying physiology with which the drug is interacting. Thus, identifying the correct physiological pathway and making an accurate drug model can give insight to interactions that the other types of models cannot detect. In short, each of these models serve varying degrees of purpose, and the correct identification of desired information can lead to the selection of the model that is best for each drug. This type of work allows for simple, informed profiles for the drugs that are under examination.

5. References

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6. Acknowledgements

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