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A Physiologically-Based Pharmacokinetic Model for Vancomycin

Rebekah White
East Tennessee State University

A Physiologically-Based Pharmacokinetic Model for Vancomycin

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Rebekah White

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Michele Joyner, Ph.D.

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ABSTRACT

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Vancomycin is an antibiotic used for the treatment of systemic infections. It is given intravenously usually every twelve or twenty-four hours. This particular drug has a medium level of boundedness, with approximately fifty percent of the drug being free and thus physiologically effective. A physiologically-based pharmacokinetic (PBPK) model was used to better understand the absorption, distribution, and elimination of the drug. Using optimal parameters, the model could be used in the future to test how various factors, such as BMI or excretion levels, might affect the concentration of the antibiotic.

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1 INTRODUCTION

The inspiration for this research into the PBPK modeling of vancomycin was based on the work and thesis of a former ETSU graduate student Whitney Forbes [6]. Her research involved the development of this type of model to study ertapenem and the effects BMI has on this drug's physiological properties. The original goal of this research was to determine if BMI affected the concentration of vancomycin in the same manner. This thesis uses a similar methodology to develop a model for the concentration of vancomycin in the body, which can later be tested across various BMI levels.

Vancomycin, depicted in Figure 1, "is an amphoteric glycopeptide antimicrobial substance produced by the growth of certain strains of Nocardia orientalis" [12, 22]. It is a broad spectrum antibiotic and the first line of defense for the treatment of methicillin-resistant Staphylococcuss aureus (MRSA). It is commonly used to treat infections of the bloodstream and skin as well as meningitis [3]. Vancomycin was isolated from soil samples collected in the jungles of Borneo by a missionary, Edmund Kornfeld, in 1953. It was soon realized that bacteria did not build up resistance to the drug as quickly as to other antibiotics such as penicillin. For this reason its name was derived from the word "vanquish" [11]. It is a moderately bound antibiotic with the protein binding of vancomycin being approximately 55%. It is primarily eliminated via the renal route, with 80%–90% recovered unchanged in urine within 24 hours after administration of a single dose. The remaining drug is eliminated in the stool. There is no apparent metabolism of the drug [19]. The average dose for an adult with healthy renal function is 1 gram every 12 or 24 hours. The infusion

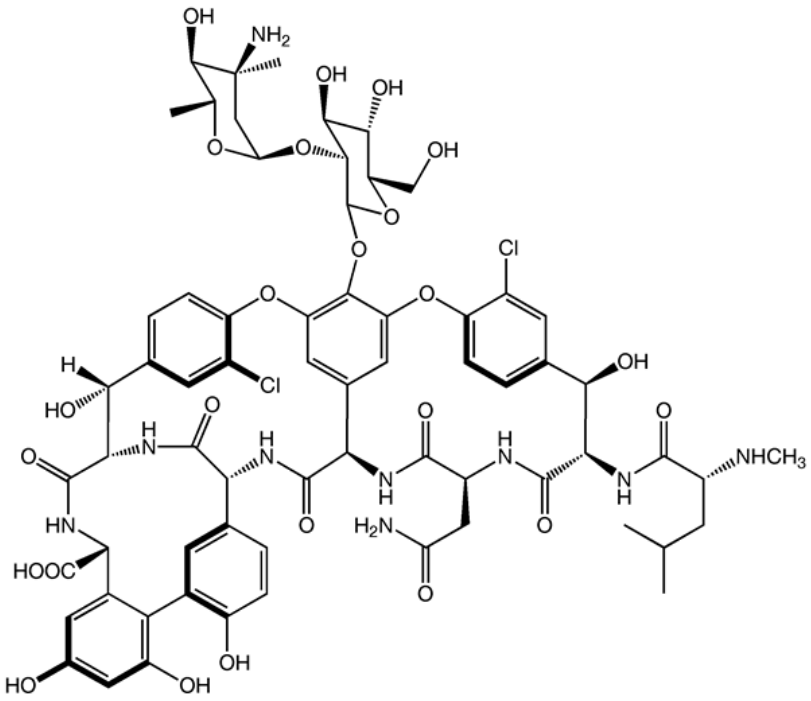

Figure 1: Vancomycin

time is 1 hour. Some important partition coefficients include its solubility in water, $S_w = 0.255$ as well as its solubility in n-octanol:water, $K_{ow} = 0.000794328$, [1]. The use of these will be clear as the model is developed.

Physiologically-based pharmacokinetic (PBPK) modeling examines how drugs are utilized by the human body by examining the factors that affect absorption, distribution, metabolism, and excretion of the drugs [3]. In building a PBPK model, one makes decisions about which compartments will be used to model the dispersion of the drug. Once this is decided, information regarding compartment volumes, flow rates, and properties of the drug being studied allow the model to be developed. In section 2 the development of this model for vancomycin is given. In sections 3, 4, and 5 we will discuss modifications made on the base model that resulted in the final

PBPK model for vancomycin.

2 THE MODEL

The first step in creating a PBPK model is to determine the compartments that will be included in the model. In order to do this, the physiological affects the drug has on different organs or tissues of the body must be known. The route of administration as well as how the drug is excreted is also required. This, combined with what aspect of the drug is to be studied, determines which compartments will be included in the model. Since the effect of BMI on absorption is the ultimate goal of this modeling effort, which means the amount of fat is relevant. Therefore, adipose tissue (F) must also be a compartment. The drug is primarily excreted in the urine, with a small amount being eliminated in the feces. This means the kidney (K) and gut (G) must comprise two compartments in the model. All other tissues (OT) are lumped into one compartment. Information about the other tissues is obtained by subtracting what is calculated regarding those five compartments from what is known about the total body. Notice this gives us five compartments, blood, fat, kidneys, gut, and other tissues. There are also two places of excretion, in the urine and feces. The schematic given by Figure 2 depicts this.

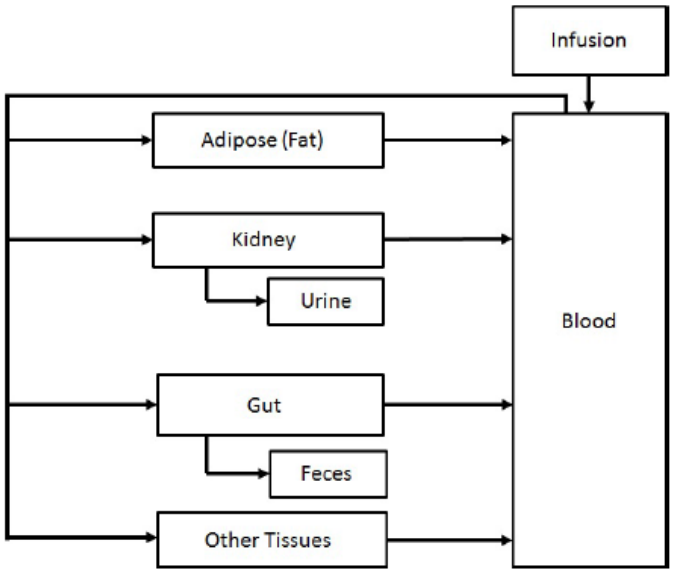

Figure 2: Model Compartments

The next step in creating the PBPK model is to examine how the drug is broken down or activated in the body. Specifically, what concentration of the drug in the blood has physiological affects on the body. A portion of the drug is bound to binding proteins in the body and rendered ineffective. What is not bound is known as the free concentration, while the inactive part is known as the bound concentration. Although the amount of boundedness of the drug can change as plasma levels increase, if a linear relationship between the two is present, the free concentration can be determined based on the total concentration. For example, vancomycin is a moderately bound drug where an increase or decrease in its free concentration is based only on the total concentration in the blood [18]. It is known that vancomycin is approximately fifty percent bound to plasma proteins. Because only the free con-

centration is flows throughout the body, we need a relationship connecting the two [7]. Together, the free concentration (C_{Bf}) and the bound concentration (C_{Bound}) make up the total concentration of vancomycin in the blood (C_{Bl}). This relationship is given by

$$C_{Bl} = C_{Bf} + C_{Bound}.$$

For this particular drug, we assume initially the free concentration is a linear function of the total concentration, but we will later assume that a nonlinear relationship exists in order to better fit the model to data (see section 5) [18]. Because of the boundedness of vancomycin, we are able to write the free concentration as a portion of the total concentration [2]. This is represented as

$$C_{Bf} = 0.51 * C_{Bl}. \tag{1}$$

The rate of infusion, R_i, represents the quantity of drug entering the body intravenously with respect to time. This is given by

$$R_I = \begin{cases} \frac{D}{T_I}, & 0 \leq t \leq T_I \\ 0, & t > T_I \end{cases} \tag{2}$$

Here, $D = 1$gm is the dosage and $T_I = 1$hr is the infusion time.

2.1 Parameters

The next part of developing the model involves determining the equations for volumes and flow rates. These provide information regarding how the drug is distributed throughout the different compartments. It is necessary to know the volumes of each compartment in order to examine drug dynamics for the entire system. Both the equations for the volumes of each compartment as well as blood flow rates are determined from literature and based on body weight (72kg) and height (1.75m) for the average male. This portion of the model takes into account body mass and will therefore allow us to examine how changes in body mass index will affect certain drug factors. These are given in Equation (3). The equations for V_{Bl} and V_K were from [17], while the equation for V_F was from [9] and V_G from [13].

$$\begin{aligned} V_{Bl} &= \frac{13.1(BH*100)+18.05(BW)-480}{0.5723} \\ V_K &= 15.4+2.04(BW)+51.8(BH)^2 \\ V_F &= 1.36*\left(\frac{BW}{BH-42}\right)*1000 \\ V_G &= 0.0171*(BW)*1000, \end{aligned} \tag{3}$$

In order to account for the remaining volume of the other tissues, V_{OT}, we will subtract from the total body volume, the volumes above. This is given by

$$V_{OT} = BW*1000-(V_{Bl}+V_F+V_K+V_G). \tag{4}$$

From here, the amount of blood flow, and consequently drug flow, through these compartments can be determined [21]. An equation for total flow rate in the body, Q_{Total}, is based upon weight [5]. The flow rates for the individual compartments can be modeled as a fraction of Q_{Total}. These percentages are found in literature and are given in Table 1.

Table 1: Parameter Values Obtained from Literature

Parameter	**Value**	**Units**	**Reference**
Q_{Total}	$235 * (BW)^{0.71} * 60$	mL/hr	[5]
Q_F	$0.052 * Q_{Total}$	mL/hr	[13]
Q_K	$0.19 * Q_{Total}$	mL/hr	[13]
Q_G	$0.17 * Q_{Total}$	mL/hr	[13]

2.2 Partition Coefficients

Another important aspect of drug dispersion that must be accounted for is how much of the drug makes it out the tissues. It may be that not all of the drug concentration that enters a tissue via the blood will leave that tissue and be recirculated. Specifically, we must know the tissue's solubility in order to determine what concentration of the drug flowing into the tissue will be trapped there. In order to take this into account, partition coefficients are created. To calculate these partition coefficients, two things from literature must be known, the solubility of the drug in water (S_w) and the solubility of the drug in n-octanol (S_0), which were given in section 1. From here, an algorithm can be used to calculate these partition coefficients, P_i, for tissue i. Blood enters and leaves a compartment in such a way as to maintain equilibrium. Thus, we defined an equilibrium partition coefficient for a tissue, i, as

$$\frac{C_i}{P_i}. \tag{5}$$

In Equation (5), C_i is the concentration in tissue i, and P_i is the partition coefficient for that tissue. Notice that the concentration of drug in the blood must be divided by a quantity in such a way as to decrease that concentration. Thus, the concentration of drug flowing into a tissue will be greater than or equal to that which is able to escape. These partition coefficients can be determined using an algorithm developed by Poulin and Krishnan [15, 16]. This is given by

$$P_t = \frac{([S_o * N_t] + [(S_w * 0.7P_t) + (S_o * 0.3P_t)] + [S_w * W_t]}{([S_o * N_b] + [(S_w * 0.7P_b) + (S_o * 0.3P_b)] + [S_w * W_b]}, \tag{6}$$

where t corresponds to the specific tissue, b to the blood, and S_w, and K_{ow} are drug specific parameters [21]. The following equation uses S_w and K_{ow} to calculate the solubility in n-octanol, S_o.

$$S_o = K_{ow} * S_w$$

.

From this we could determine that $S_o = 0.000178724$. The partition coefficients calculated from Equation (6) for each tissue in the model is given in Table 2. These values will be considered further in section 3.

Table 2: Partition Coefficients

Parameter	Value
P_F	0.0009
P_K	0.9767
P_G	0.8899
P_{OT}	0.9449

The last portion of creating the model involves relating all of the information about the flow rates, volumes, and partition coefficients of all the tissues that make up the compartments. Next, the model is condensed to systems of differential equations. This is possible as the drug acts essentially as a rate of flow with respect to time, entering and leaving each compartment. For example, consider Figure 3.

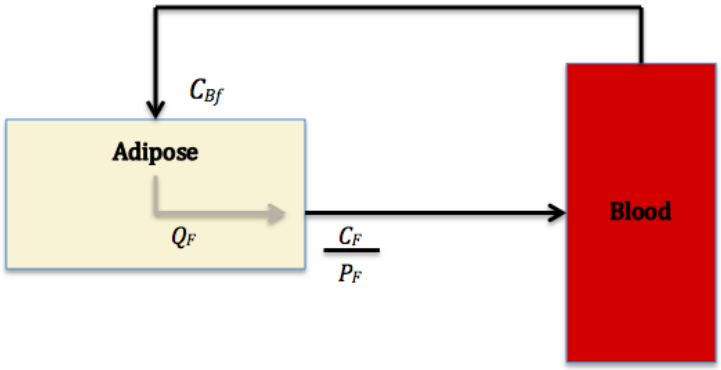

Figure 3: Fat to Blood Differential

This depicts the flow between the fat and blood compartments. This can be modeled as a first order differential equation [20], which is explicitly given as

$$V_F \frac{dC_F}{dt} = Q_F \left(C_{Bf} - \frac{C_F}{P_F} \right).$$

The Q_F represents the flow rate through the fat compartment. The C_{Bf} represents the concentration of drug flowing into the compartment, while the $\frac{C_i}{P_i}$ represents the portion of this same concentration flowing out. Notice that the flow rate times the difference in the entering and exiting concentrations is equal to the rate of change of the drug concentration times the volume of the compartment.

The kidneys and gut work similarly except that the quantity excreted from the body system must be taken into account here by subtracting the rate of excretion times the concentration being excreted. The model assumes a linear rate of excretion. For instance the rate of urinary excretion, $\frac{dA_u}{dt}$, could be represented by the equation below.

$$\frac{dA_U}{dt} = k_U C_K$$

Notice this rate is equal to the constant parameter, k_U, times the concentration excreted from the kidneys. The blood compartment takes into account the initial infusion quantity along with the recirculation quantities that are emitted from the other compartments. For instance the portion of drug that escaped the adipose tissue will re-enter the blood and thus circulate through the compartments again. The quantities of excretion are also calculated in order to compare with literature data. The initial conditions are zero as it is assumed there is no initial concentration of vancomycin in the blood. The model consists of these systems of first-order differentials being solved simultaneously at different time steps to provide drug concentrations for the antibiotic in the body, given the assuptions in the modeling process. This can

then be compared to literature data and the error in the model can be examined [4]. The system of equations that describe this specific system are given by Equation (7).

$$\begin{aligned}
V_F\frac{dC_F}{dt} &= Q_F\left(C_{Bf}-\frac{C_F}{P_F}\right)\\
V_K\frac{dC_K}{dt} &= Q_K\left(C_{Bf}-\frac{C_K}{P_K}\right)-k_UC_K\\
V_G\frac{dC_G}{dt} &= Q_G\left(C_{Bf}-\frac{C_G}{P_G}\right)-k_FC_G\\
V_{OT}\frac{dC_{OT}}{dt} &= Q_{OT}\left(C_{Bf}-\frac{C_{OT}}{P_{OT}}\right)\\
V_{Bl}\frac{dC_{Bl}}{dt} &= Q_F\frac{C_F}{P_F}+Q_K\frac{C_K}{P_K}+Q_G\frac{C_G}{P_G}+Q_{OT}\frac{C_{OT}}{P_{OT}}-Q_{Total}C_{Bf}+R_I\\
\frac{dA_U}{dt} &= k_UC_K\\
\frac{dA_F}{dt} &= k_FC_G,
\end{aligned} \tag{7}$$

Notice in the equations given above, the only parameter values not gathered from data or explicitly calculated are k_U and k_F. These will be estimated in section 2.3. Table 3 lists all the parameters and variables for this model.

Table 3: Model Variables and Parameters

Symbol	Description	Units
C_i	Concentration of vancomycin in tissue i	mcg/mL
C_{Bf}	Concentration of free vancomycin in the blood	mcg/mL
A_U	Amount of vancomycin in the urine	mcg
A_F	Amount of vancomycin in the feces	mcg
V_i	Volume of tissue i	mL
Q_i	Flow rate in tissue i	mL/hr
α	Infusion Coefficient	dimensionless
t	Time	hr
P_i	Blood partition coefficient in tissue i	dimensionless
BW	Body Weight	kg
BH	Body Height	m
R_i	Rate of Infusion	mcg/hr
D	Dose	mcg
T_i	Length of infusion	hr
k_U	First-order rate constant of urine excretion	mL/hr
k_F	First-order rate constant of feces excretion	mL/hr

2.3 Inverse Problem

PBPK modeling makes use of known physiological parameters such as blood flow rates through particular tissues, body weight, and organ volumes. It also incorporates estimated parameter values such as rate of excretion in urine (k_u) and feces (k_F). In order to determine which values for these parameters optimize the model so as to mimic the data found in literature, a least squares inverse problem is used. This will compare differences between our literature blood concentration values versus those the model outputs for different values of k_U and k_F. This is depicted in Equation (8), where $q = [k_u \quad k_f]$ represents the parameters to be estimated. The value of the cost

function is given as

$$J(q) = \left(\sum_{j=1}^{N} \left(\frac{\hat{y}_i - C_{Bl}(t,q))}{C_{Bl}(t,q)} \right)^2 + \left(\frac{0.8 - A_U(24)}{A_U(24)} \right)^2 \right). \tag{8}$$

The smaller this value is, the more closely the model output will fit the literature data.

The clinical data was obtained by extracting data from a graph using the *grabit* program in Matlab [4, 10]. This data is given in Table 4. In order to determine which values of q provide the smallest J, a built in Matlab function, *fminsearch*, was used. It uses a Nelder-Mead algorithm to estimate parameters based off an initial guess for the parameters. J is calculated by summing the squared differences between the model output given parameters q and the literature data. This allows us to determine the relative error in our model. From here, the software will try parameter values generated using the Nelder-Mead algorithm and repeat the calculations. If the new J value is better than the previous, it will continue to guess values in that same direction. It may also choose values in the other direction to ensure that it has chosen estimates that minimize the cost function. Once the program reaches a certain threshold, it outputs the optimal parameter values. These optimizing values will then be used in the model.

Table 4: Clinical Data for the Total Concentration of Vancomycin[4]

Time (t_j) (hrs)	Clinical Data (C_{Bl}) (mcg/mL)
1	63.61
1.08	53.67
1.25	46.39
1.50	38.44
2.00	29.17
2.50	24.32
3.00	21.01
3.40	18.14
4.00	15.28
5.00	12.86
7.00	9.35
9.00	6.72
13.00	4.77

2.4 Results

After running the cost function with the initial guess of $q = [10000 \quad 1000]$ (values of k_U and k_F respectively), the *fminsearch* program determined that the optimal parameter values are $k_U = 9,993\frac{mL}{hr}$ and $k_F = 1,691\frac{mL}{hr}$. This gave the cost function a value of $J(q) = 1.318$. This value represents the sum of squared relative errors across all the data points and excretion levels and implies the model has approximately 130% squared error. Figure 4 depicts the urine excretion over the dosing period. This is of importance as this is the primary route of elimination of vancomycin from the body. Clinical data puts urine excretion at 80% of the initial dose. The model predicted 79.6% for urine excretion. The percent error between these two is 0.495%. This tells us that the model depiction of drug excretion is very accurate. The remaining drug in

the body is eliminated via the gut, as virtually no amount of the drug is metabolized.

Figure 4: Urine Excretion

Figure 5 provides a graphical depiction of the model output for blood concentration versus the clinical data over the twelve hour period following the end of infusion. The percent relative error in point estimates for the total concentration is 47.59%. This is certainly too high a value for relative error. Notice on the graph that the highest peak is not in line with the data. This is the area of least fit for the model. The only area of the data that is in line with model output is at the end of the dosing period.

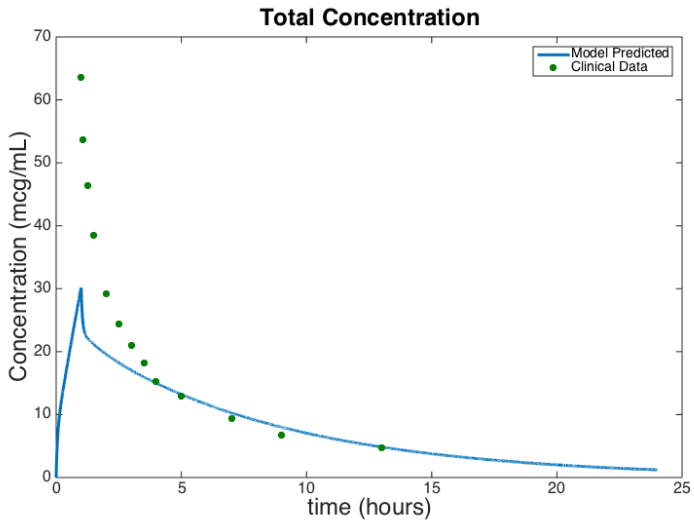

Figure 5: Total Concentration

3 THE MODEL WITH PARTITION COEFFICIENTS AS PARAMETERS

The fit depicted in figure in the previous results is not accurate enough to conclude our model is a good representation of how vancomycin acts on the human body. It may be noted that the partition coefficients in Table 2 are all values less than one. Referring back to Equation (5), it is determined that those values do not make biological sense as they would imply that a higher concentration of the drug is leaving the tissues than what entered. This is likely due to the fact that the solubility in water and n-octanol were approximated using computer software [1]. In order to improve the model, these partition coefficients will be estimated as parameters, rather than calculated from a formula. In order to determine which of these partition coefficients has the greatest effect on blood concentration, sensitivity analysis was done. In order to do this, the partial of each Equation in (7) had to be taken with respect to each of

the six parameter values. This allows us to determine the effect each parameter has on the concentration in each compartment. The calculation is done by normalizing the sensitivities using the modified L_2 norm

$$\left|\left|\frac{\partial C_{tissue}}{\partial q_j}\right|\right|_2 = \left[\frac{1}{t_f - t_0}\int_{t_0}^{t_f}\left(\frac{\partial C_{tissue}}{\partial q_j}\right)^2 dt\right]^{\frac{1}{2}} \frac{q_j}{maxC_{tissue}}. \tag{9}$$

Using Equation (3), results of these calculations are depicted below [6].

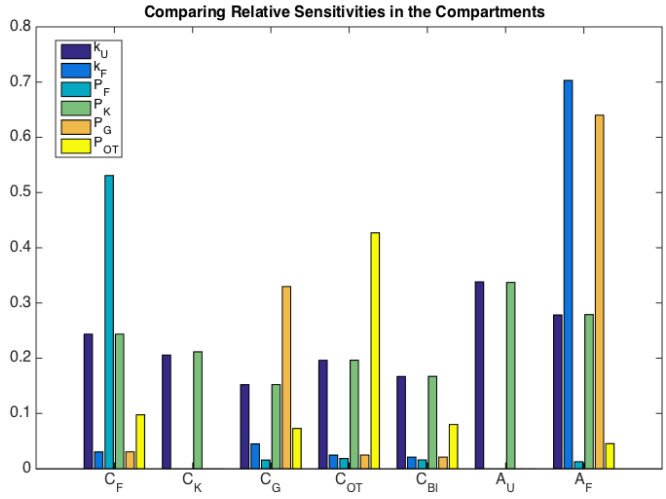

Figure 6: Sensitivity Analysis

The results showed no particular partition coefficient dominated the behavior of blood concentration over time in the various compartments. Thus, all partition coefficients would need to be estimated as parameters. We use the same cost function given by Equation (8). Our input parameters are given by $q = [P_F \quad P_K \quad P_G \quad P_{OT} \quad k_u \quad k_f]$. As previously mentioned, the partition coefficients should not be values below one. Thus, we bound them to be greater than or equal to one during the minimization. The

result of this change is given in Figure 7. The ending optimal parameter estimates for the partition coefficients are essentially equal to 1. It estimates $k_U = 8,298\frac{mL}{hr}$ and $k_F = 1,212\frac{mL}{hr}$.

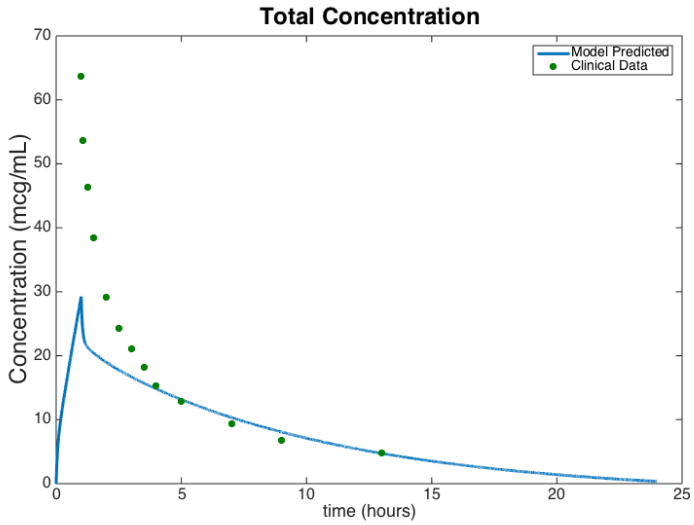

Figure 7: Total Concentration With Partition Coefficients as Parameters

It is clear that this does not solve the problem of the peak being too low. Furthermore, as the estimates for the partition coefficients, P_F, P_K, P_G, P_{OT}, were approximately one, we will remove these as parameters and instead set them equal to 1. The next section will discuss alternative changes to be made to the model in order to better improve the fit.

4 THE MODEL WITH AN INFUSION COEFFICIENT

As noted in the previous section, our model falls short in predicting the accurate peak of vancomycin concentration in the blood. For this reason, a new parameter α

is introduced into the model as was done in [6]. This parameter acts as an infusion coefficient, slowing the rate of drug dispersion throughout the compartments during the infusion period. The infusion coefficient, α, is given by

$$\alpha = \begin{cases} \alpha_I, & 0 < t \leq T_I \\ 1, & T_I < t < 12 \end{cases} .$$

This makes sense biologically as the quantity of vancomycin traveling through the various compartments may not reach its maximum until the entire dose of the drug has been administered. In addition, the way in which the drug binds during infusion may be different than the way it binds once the entire dose is administered. This changed the system of Equations in (7) by replacing C_{Bf} by $\alpha * C_{bf}$ where $\alpha = 1$ after the infusion period and is an unknown parameter during the infusion period, which we will estimate. Now $q = [k_u \quad k_f \quad \alpha]$, with an initial guess of $\alpha = 0.35$. The minimization algorithm was run again to determine the optimal parameter estimates. The estimate for α was given as 0.313, and $k_U = 10,306\frac{mL}{hr}$ and $k_F = 1,770\frac{mL}{hr}$. The solution curve for the model is plotted with the data in Figure 8. The ending cost function value was $J = 0.866$. The percent relative error in point estimates for total concentration was 33.53%.

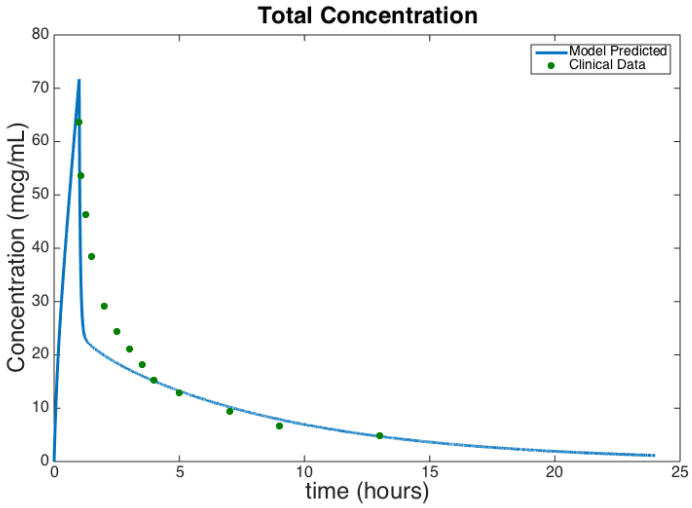

Figure 8: Total Concentration With Infusion Coefficient

Notice that although the addition of α as a parameter into the model did allow for the correct concentration peak, during the times following the peak but before the blood concentration levels out, the model does not fit the data well. A non-linear excretion in the urine was implemented to try to fix this problem but the effects were negligible. The following section discusses the next steps taken to better the model.

5 THE MODEL WITH NONLINEAR BLOOD CONCENTRATIONS

From the results given in Figure 8 it is clear that the peak blood concentration of the model output as well as the ending blood concentrations match the literature data fairly well. We believe the problem is in the linearity of the model during the middle of the timespan. One possible explanation for this is that the binding of the drug is not entirely linear. That is, Equation (1) is a linear approximation to

a nonlinear relationship between the free and bound concentrations of the drug in the blood. To test this hypothesis, a nonlinear Michaelis-Menten equation is used to model the bound concentration. This equation is given by

$$C_{Bound} = \frac{B_m C_{Bf}}{K_d + C_{Bf}}. \tag{10}$$

Here, B_m represents the blood receptor content and K_d the dissociation constant [14]. Because the total blood concentration is the sum of the free and bound concentrations, using Equation (10) given above we have that

$$C_{Bl} = C_{Bf} + \frac{B_m C_{Bf}}{K_d + C_{Bf}}. \tag{11}$$

As seen in Equation (11), it is not necessary to directly calculate the bound concentration of the drug in order to study the total and free concentrations in the blood. Algebraic manipulation results in the following equation, which provides the free concentration as a function of C_{Bl}, B_m, and K_d

$$C_{Bf} = \frac{C_{Bl} - B_m - K_d + \sqrt{(B_m + K_d - C_{Bl})^2 + 4K_d C_{Bl}}}{2}. \tag{12}$$

Notice there are now two additional parameters B_m and K_d. Using Equation (12) for the free concentration in the model (Eq. (2)) along with the modified version with the parameter α, we estimate the parameters. We use $q = [B_m \quad K_d \quad k_u \quad k_f \quad \alpha]$ in the cost function (Eq. (8)). The results of doing this are given by Figure 9. It is clear that the nonlinear blood concentration approach provides the most accurate model. To verify, the cost function value after the minimization is $J = 0.343$. This is the smallest value of J so far in the model development.

Table 5: Results

Literature Concentrations [4]	Model Approximations	Percent Error
(mcg/mL)	(mcg/mL)	%
63.61	68.46	7.6
53.67	44.99	16.2
46.39	33.89	26.9
38.44	30.80	19.9
29.17	27.40	6.1
24.32	24.61	1.2
21.012	22.21	5.7
18.15	20.10	10.7
15.28	18.21	19.2
12.86	15.00	16.6
9.35	10.19	9.0
6.73	6.93	3.1
4.77	3.21	32.7
Exact Urine Excretion (mcg/mL)	Approximate Urine Excretion (mcg/mL)	Percent Error %
0.800000	0.800078	0.0097%

These results can be visualized by Figure 9.

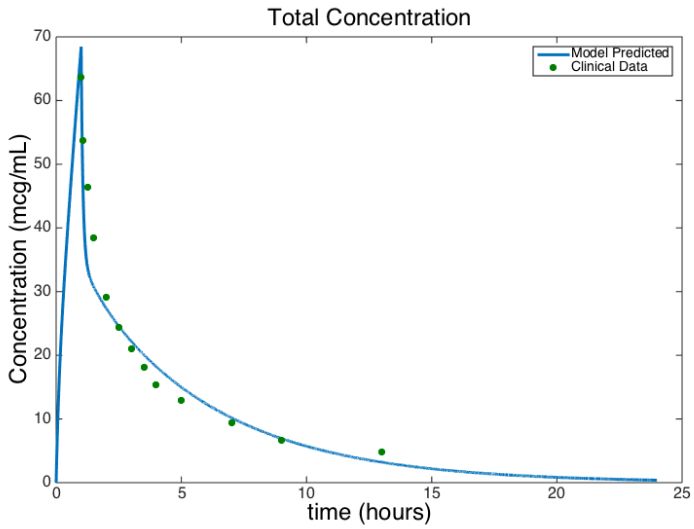

Figure 9: Nonlinear Total Concentration

There are other import pieces of data resulting from the final model that will be useful in future analysis. The model provided us with the area under the curve (AUC), which is 184. This information is important as it relates again to renal toxicity. Having too large an area could increase the risk of renal failure or other harmful side effects of the drug. The ratio between AUC and minimum inhibitory concentration (MIC) is also significant in trying to determine the most effective dosing. Specifically, it has been related to vancomycin's effectiveness in treating staph infections [8]. The lowest concentration level given by the model does not fit the lowest blood concentration as seen in Table 5. This value is of importance as the next dose would begin at the end of the first dosing period in such a way as to ensure that this level does not fall below the MIC in order to prevent resistance development. This is also the area of focus when adjusting body mass. Specifically, one may be interested in whether or not differing BMIs will cause blood concentration levels to

drop below the MIC.

6 CONCLUSIONS

The development of a model that provides comparable information to measure the absorption, distribution, and elimination of vancomycin provides a solid base for continued research regarding this drug. Specifically, it will allow for examination into the physiological effects body mass has on these drug factors. Because compartment volume is based of body mass, we are able to adjust these volumes according to changes in body mass and produce model predictions based on differing body masses. We may also be interested in differences between male and female absorption. These could also be related to compartment volume as the average body mass for males and females differ from one another. Another aspect of future work will be in improving the accuracy of the model even further. One way is in evaluating the reliability of the parameters estimated. Some of the parameters gathered from literature did not provide useful information when input into the model. For instance, the solubility in water and n-octanol:water of vancomycin was gathered from literature but did not provide for biologically possible partition coefficients. For vancomycin, the lack of data regarding its chemical properties as well data on the blood concentrations after infusion posed some problems in developing an accurate model. Throughout the development of the model until its final version, the parameters being estimated changed as the model was modified. In the future, statistical analysis could be implemented to determine confidence intervals for the parameters being estimated. This would provide information about the degree to which the model could vary based on changing

parameters values. Overall, modifying a PBPK model for ertapenem resulted in a reliable model of the absorption, distribution, and elimination of vacomycin [6]. The model produced results for blood concentrations with less than a total of 15.96% error in point estimates and less than 0.0097% error in urine excretion levels.

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