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Research article

Modeling Ertapenem: the impact of body mass index on distribution of the antibiotic in the body

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Abstract: Ertapenem is an antibiotic commonly used to treat a broad spectrum of infections and is part of a broader class of antibiotics called carbapenems. Unlike other carbapenems, ertapenem has a longer half-life and thus only has to be administered once a day. Previously, a physiologically-based pharmacokinetic (PBPK) model was developed to investigate the uptake, distribution, and elimination of ertapenem following a single one gram dose in normal height, normal weight males. Due to the absorption properties of ertapenem, the amount of fat in the body can influence how the drug binds, how quickly the drug passes through the body, and thus how effective the drug might be. Thus, we have revised the model so that it is applicable to males and females of differing body mass index (BMI). Simulations were performed to consider the distribution of the antibiotic in males and females with varying body mass indexes. These results could help to determine if there is a need for altered dosing regimens in the future.

Keywords: Ertapenem; physiologically based pharmacokinetic model (PBPK); Body Mass Index (BMI); Dosage; AUC; peak concentration

1. Introduction

Ertapenem, an antibiotic commonly used to treat community-acquired and mixed infections, is part of the class of antimicrobials called carbapenems [10, 12]. Carbapenems have the widest spectrum of antimicrobial activity against both gram-positive and gram-negative bacteria [6, 16]. Unlike other carbapenems which have a half-life of approximately one hour and must be administered several times

a day, ertapenem has a half-life of approximately four hours and can thus be administered just once a day. This antibiotic is usually administered intravenously over a thirty minute period to individuals who are hospitalized due to an infection.

Previously, a PBPK model was developed to investigate the absorption, distribution, and elimination of the antibiotic ertapenem in normal height, normal weight males [7]. Because of the way ertapenem is absorbed, the amount of fat in the body can influence how the drug binds, how quickly the drug passes through the body, and thus how effective the drug is. Our work in this paper focuses on determining if body height and body weight should play a role in the antibiotic dosage.

BMI, or Quetelet's index, is the ratio of weight, BW, (in kilograms) to the square of the height, BH, (in meters),

$$BMI = \frac{BW}{BH^2}.$$

This index is often used as it has a high correlation with body fat percentage and a low correlation with body height [4] and is typically used to classify adults into different categories. The five classifications of BMI we considered are given in Table 1.

Table 1. Classifications of BMI.

Classification	BMI
Underweight	< 18.5
Healthy (Normal)	18.5-25
Overweight	25.1-30
Obese	30.1-40
Severely Obese	40.1-50

In this article, we seek to investigate the uptake, distribution, and elimination of ertapenem following a single one gram intravenous dose in males and females of varying BMI. We begin in Section 2 with the revision of the physiologically-based pharmacokinetic (PBPK) model for males of various heights and weights and the optimizations that were performed to estimate the unknown parameters in the model. Equation changes applicable to females are introduced in Section 3. In Section 4, results of numerical simulations for the distribution of the antibiotic in males and females with varying BMI are presented. We will conclude with some final remarks in Section 5.

2. Model structure and modifications

2.1. Original model

Pharmacokinetic modeling seeks to examine factors that affect absorption, distribution, metabolism, and excretion [2]. PBPK modeling incorporates known physiological parameters such as body weight, organ volumes, and blood flow rates in particular tissues. In the previously developed model for ertapenem, we focused our attention on the tissues and organs most affected by the drug; a summary of the model as shown in Figure 1 is presented here but we refer the reader to Joyner et al. for more details [7].

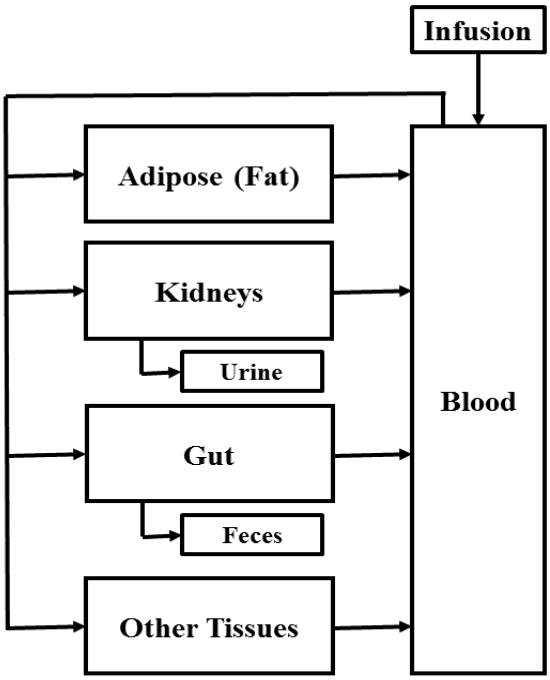


Figure 1. Schematic of the model [7].

The PBPK model has separate compartments representing the blood (Bl), kidneys (K), adipose or fat (F), the gut (G), and other aggregated tissues (OT) as well as the urine (u) and the feces (f). Urine and feces excretion are considered to occur at linear rates and are represented by $k_u C_K$ and $k_f C_G$, respectively, where k_u and k_f are the first-order linear rate constants for excretion and C_K and C_G represent the concentrations of ertapenem in the kidneys and gut. Intravenous (IV) dosing is described by infusion directly into the blood compartment.

Ertapenem is highly bound to human plasma proteins. Only the free, unbound portion of the drug actually saturates the tissues and can be excreted [2]. Moreover, since only the free, or unbound, concentration of the drug is considered to be medicinally effective, we chose to examine both the total concentration and the free concentration in the blood. The total blood concentration, C_{Bl}, is comprised of both the free concentration (C_{Bf}) and the bound concentration (C_{Bound}),

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

As outlined in [7], the formula for the free concentration can be written as

$$C_{Bf} = \frac{C_{Bl} - B_m - K_d + \sqrt{(B_m + K_d - C_{Bl})^2 + 4K_d C_{Bl}}}{2}, \tag{1}$$

where B_m is the density of binding sites and K_d is the dissociation constant [8, 14].

The compartment volumes (given in milliliters) were based on body height and body weight for males; the calculations for V_{Bl} and V_K were obtained from [15] whereas the one for V_F was from [9] and V_G was from [13]. The equations for compartment volumes are given by

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

During infusion, the blood flow rate from the blood into each tissue compartment was multiplied by a constant value between 0 and 1, which is referred to as α_I, and after infusion, the infusion coefficient is set equal to 1. Thus, the infusion constant α is defined by

$$\alpha = \begin{cases} \alpha_I, & 0 < t \le T_I \\ 1, & T_I < t < 24 \end{cases},$$

where T_I is the length of infusion. During the infusion, the rate of infusion is given by

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

where D is the dosage and T_I is the length of infusion.

The total rate flow in the body was calculated using the subject's body weight [3],

$$Q_{Total} = 235*(BW)^{0.71}*60.$$

The flow rates for the adipose, kidney, and gut compartments were a percentage of Q_{Total}. It was assumed that the concentration in the venous blood leaving the compartment was at equilibrium with the concentration in the compartment, with P_i being the equilibrium partition coefficient for tissue i:

$$C_{venous} = \frac{C_i}{P_i}.$$

The full model for the system is given in Equation (3) [7]:

$$\begin{aligned} V_F\frac{dC_F}{dt} &= Q_F\left(\alpha C_{Bf}-\frac{C_F}{P_F}\right) \\ V_K\frac{dC_K}{dt} &= Q_K\left(\alpha C_{Bf}-\frac{C_K}{P_K}\right)-k_uC_K \\ V_G\frac{dC_G}{dt} &= Q_G\left(\alpha C_{Bf}-\frac{C_G}{P_G}\right)-k_fC_G \\ V_{OT}\frac{dC_{OT}}{dt} &= Q_{OT}\left(\alpha C_{Bf}-\frac{C_{OT}}{P_{OT}}\right) \\ V_{Bl}\frac{dC_{Bl}}{dt} &= Q_F\frac{C_F}{P_F}+Q_K\frac{C_K}{P_K}+Q_G\frac{C_G}{P_G}+Q_{OT}\frac{C_{OT}}{P_{OT}}-\alpha Q_{Total}C_{Bf}+R_I \end{aligned} \tag{3}$$

$$\frac{dA_u}{dt} = k_u C_K$$
$$\frac{dA_f}{dt} = k_f C_G,$$

where C_{Bf} and R_I are given by Equations (1) and (2), respectively. We assumed there were no background levels of ertapenem in the body, so all initial conditions were zero. The variables and parameters for the model are summarized in Table 2.

Table 2. Definitions of model variables and parameters.

Symbol	Description	Units
C_i	Concentration of ertapenem in tissue i	mcg/mL
C_{Bf}	Concentration of free ertapenem in the blood	mcg/mL
A_u	Amount of ertapenem in urine	mcg
A_f	Amount of ertapenem in feces	mcg
V_i	Volume of tissue i	mL
Q_i	Flow Rate in tissue i	mL/hr
t	Time	hr
P_i	Blood partition coefficient of tissue i	dimensionless
BW	Body Weight	kg
BH	Body Height	m
α	Infusion Coefficient	dimensionless
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
B_m	Blood receptor constant	mcg/mL
K_d	Dissociation constant	mcg/mL

2.2. Modification of volume of the fat equation

Previous work focused only on the use of the model for normal height, normal weight males. Thus, prior to using this model for individuals of varying height and weight, we analyzed the equations to ensure all were still applicable. The equation for the volume of the fat, Equation (4), was from work by Kvist et al. [9],

$$V_F = \left(1.36 * \frac{BW}{BH} - 42\right) * 1000. \tag{4}$$

The equation was developed based on analysis of male subjects that underwent computed tomography (CT) scans to determine their total fat volumes; these subjects had a BMI range of 31.5 ± 7.3 [9]. This range only spans high normal to obese BMI values. Thus, it is not surprising that the equation cannot accurately predict fat volumes for individuals with lower BMI. In fact, the equation results in negative values for V_F given lower BMI values; see Figure 2.

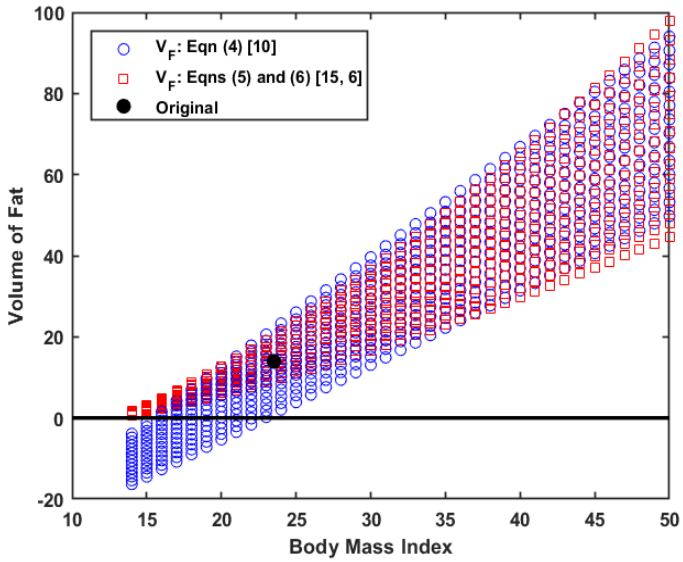


Figure 2. Plot of BMI versus volume of the fat using Equation (4) and Equations (5) and (6). The black circle is representative of the calculation done for the original normal height, normal weight male.

Given that V_F cannot be negative, we investigated other ways to represent this volume. Thus, equations relating fat volume and body fat percentage were explored. Body fat percentage (denoted as $\%BF$) is the percentage of a subject that is composed of adipose tissue. Using

$$V_F = \frac{\left(\frac{\%BF}{100} * BW\right)}{0.923}, \tag{5}$$

as given by Price el al. [15], coupled with an equation to compute body fat percentage

$$\begin{aligned} \%BF &= -96.07 + (76.91 * log_{10}(BMI)) \\ &\quad +(6.65 * log_{10}(Age)) + (11.40 * Sex), \end{aligned} \tag{6}$$

given by Fuster-Parra et al. [5], where Sex is 0 for males and 1 for females and Age is in years (an age of 39 years is used throughout this paper), we obtain a calculation for volume of the fat that can be used across all BMI. Figure 2 shows a comparison of the volume of the fat calculation using the original equation by Kvist (Equation (4)) versus the new calculation using the Price and Fuster-Parra et al. equations (Equations (5) and (6)). Since there are multiple combinations of BH and BW that produce the same BMI, we see variations in the volume of the fat for a given BMI, due to the fact that Equation (4) depends on BH and BW and Equation (5) incorporates BW and, separately, BMI in Equation (6). We note that both have good agreement for higher BMI values, but Equations (5) and (6) eliminate the problem of negative values of V_F for lower BMI values.

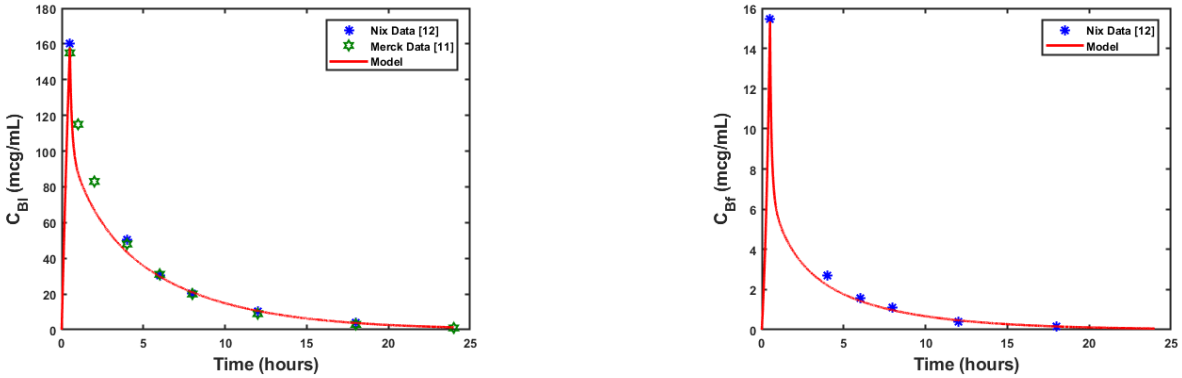
2.3. *Parameter estimation*

The model given by Equations (1)–(3) contains five unknown parameters (K_d, B_m, α_I, k_u, and k_f). Given the changes in the volume of the fat equation in the model, new estimates were obtained. Mean plasma concentrations of total and free (unbound) ertapenem at corresponding time points were approximated from graphical data given for healthy adult subjects in Nix et al. [12] using an extraction program [17]. As was done previously, we split the parameter estimation problem into two parts: (1) estimation of K_d and B_m, and (2) estimation of α_I, k_u, and k_f. Parameters K_d and B_m only appear in the relationship between the free and total concentration; therefore, it is not necessary to use the entire model to determine these parameters. The parameters were estimated using an iterative weighted least squares algorithm outlined by Banks et al. [1]. These values along with the estimated parameter values and confidence intervals using the bootstrap method ([1]) are given in Table 3.

Table 3. Parameter estimates.

$\hat{q}$	IWLS Est	Bootstrap Est	SE	90% CI
B_m ($\frac{mcg}{mL}$)	243.2	259.5	56.8	[175.6, 343.4]
K_d ($\frac{mcg}{mL}$)	10.9	11.7	3.1	[7.2, 16.2]
α_I (unitless)	0.35	0.29	0.19	[0.01, 0.57]
k_u ($\frac{mL}{hr}$)	69459	75120	20106	[45443, 104797]
k_f ($\frac{mL}{hr}$)	9612	8174	4299	[1829, 14519]

Figure 3 shows the simulation of the model in Equations (1)–(3) using the optimal parameter values from the iterative weighted least squares method with the data; additional total concentration data from Merck & Co. [11] was also plotted in order to compare to data that was not used in the optimization. The urine excretion is estimated as approximately 80%, the same as the clinical average. The model has an average 7.2% relative point error when compared to the data.



(a) Total Concentration

(b) Free Concentration

Figure 3. Simulation of Equations (1)–(3) using optimal IWLS parameter values given in Table 3. Plot (a) illustrates the total concentration C_{Bl}. Plot (b) illustrates the free concentration C_{Bf}.

3. Model differences for females

Most all of the model equations apply to males and females. The calculation of percentage of body fat, given by Equation (6), changes slightly as the Sex parameter is 0 for males and 1 for females. Additionally, a different equation is used for the volume of the blood for females [15],

$$V_{Bl} = \frac{35.5(BH * 100) + 2.27(BW) - 3382}{0.6178}. \tag{7}$$

For an initial comparison of males and females, we considered normal height, normal weight individuals. For males, we used a body height of 1.75 meters and a weight of 72 kilograms; for females, a body height of 1.62 meters and a body weight 61 kilograms were used, resulting in the same BMI for both males and females. Figure 4 shows that a normal height, normal weight male has a smaller amount in the fat throughout the 24 hour period than a female whereas Figure 5 shows females have a higher peak of both free and total concentrations than males. Nix et al. noted that in women there is "higher end-of infusion concentration," which is a characteristic that is also exhibited in the model results [12]. (A more detailed comparison of this difference can be seen later in the text in Figure 9.)

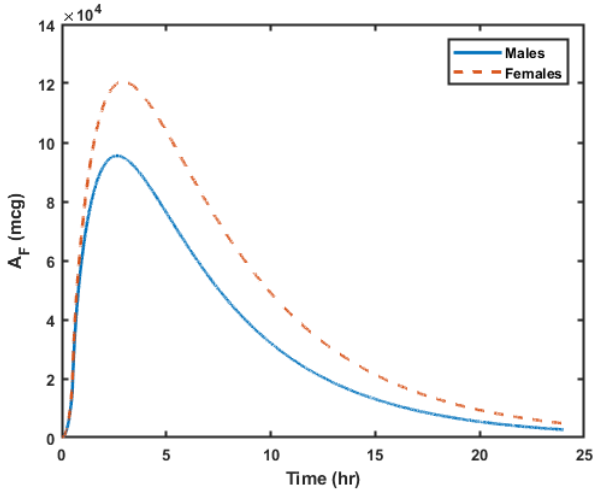
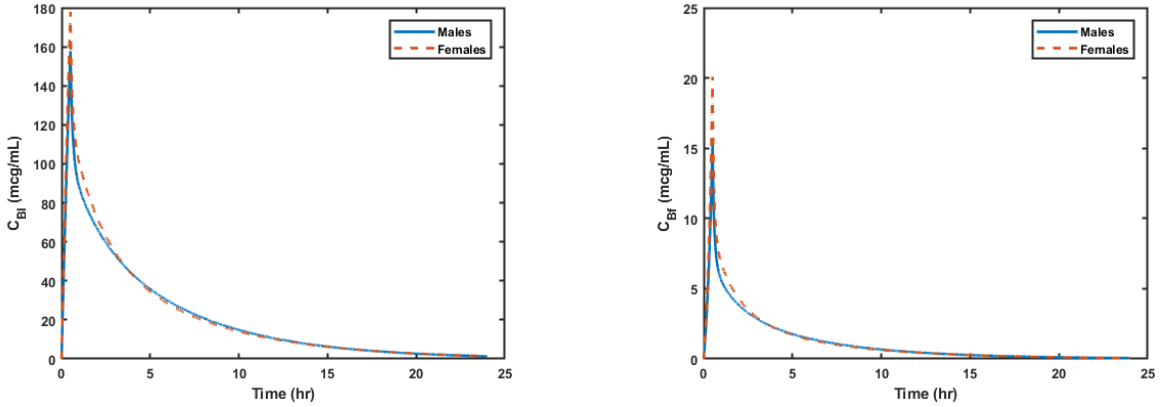


Figure 4. Amount of Ertapenem in the Fat in normal height, normal weight males and females.

4. Varying body mass index

For each of the BMI classifications given in Table 1, we analyzed the area under the curve of the total concentration in the blood as well as the area under the curve of the free concentration in the blood, the peak total concentration in the blood, the minimum free concentration in the blood, and



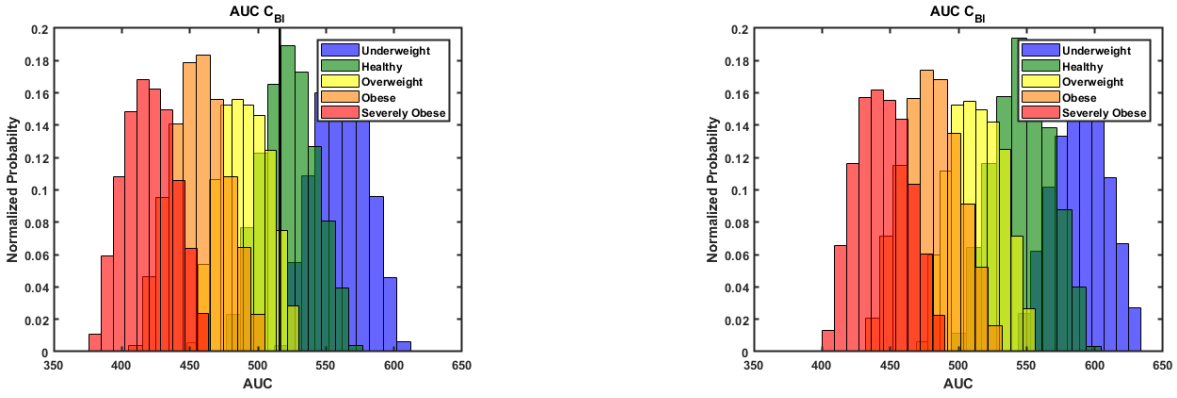
(a) Total Concentration **(b)** Free Concentration

Figure 5. Plot (a) illustrates the total concentration C_{Bl} in normal height, normal weight males and females. Plot (b) illustrates the free concentration C_{Bf} in normal height, normal weight males and females.

the amount in the fat. In each of the Figures 6–10A and Figure 11, we indicate the values for the original model fitted to the data for normal height, normal weight males as described in Section 2.1. Figure 6 shows the area under the curve of the total concentration of ertapenem in the blood for adult males and females. Although the results are similar for males and females, we note that females have a higher range of concentrations than males. We also observe that for both males and females with higher BMI, there is a lower area under the total concentration curve and a lower area under the free concentration curve (see Figure 7); this could lead to potentially less effective antibiotics. Additionally, those with higher BMI have a higher minimum free concentration (see Figure 8), so there is less chance of developing resistant bacteria. For individuals with lower BMI, there is a higher area under the total concentration curve and a lower minimum free concentration, which could lead to a greater probability of undesired side effects and the potential for development of antibiotic resistance. As seen in Figure 9, we note that people with lower BMI also had higher peak total concentrations than those with higher BMI; additionally, females had substantially higher peak concentrations than males.

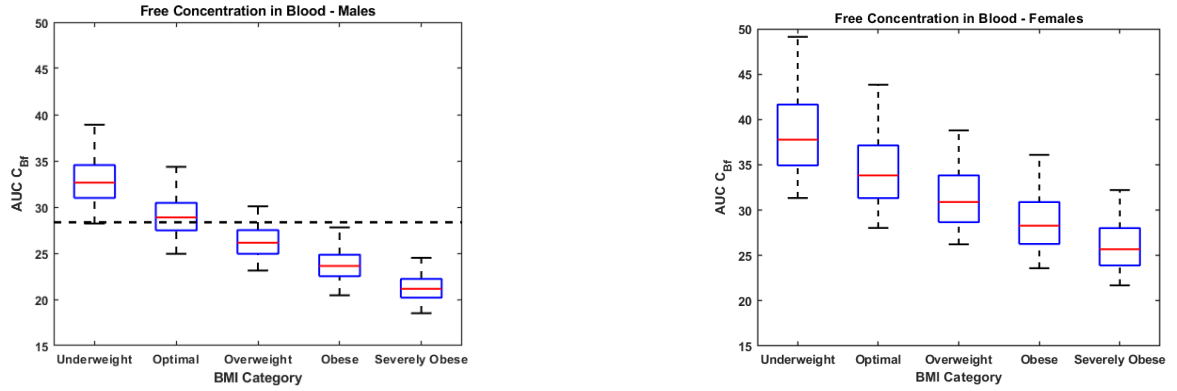
We note that in both males and females, a significant percentage of ertapenem stays in the fat during the 24 hours (See Figure 10). Thus, this portion of the dose is not circulating in the blood and is not contributing to the effectiveness of the drug.

Additionally, we examined the half-life of ertapenem in individuals of each BMI classification. As previously noted, ertapenem has a half-life of approximately four to five hours due to high protein binding [6, 16], but in studies of men and women, Nix et al. note that the half-life of ertapenem in women averaged 3.6 hours compared with 4.4 hours in men [12]. Figure 11 shows the half-life results using the model described in Equations (1)–(3) and (5)–(7). Although the half-life found in the model simulations are significantly lower than those cited in the literature, we do see differences between males and females as was found by Nix et al. as well as significant differences in males of different BMI (see Figure 11). We note that in females, BMI does not seem to effect the half-life drastically. However, for males, the half-life of the antibiotic increases as the BMI increases, indicating the drug is staying in the body longer.



(a) Males **(b)** Females

Figure 6. Area under the Total Concentration Curve of Ertapenem in the Blood. Plot (a) illustrates the distribution of AUC for males; the solid black vertical line represents the AUC for the original normal height, normal weight male. Plot (b) illustrates the distribution of AUC for females.

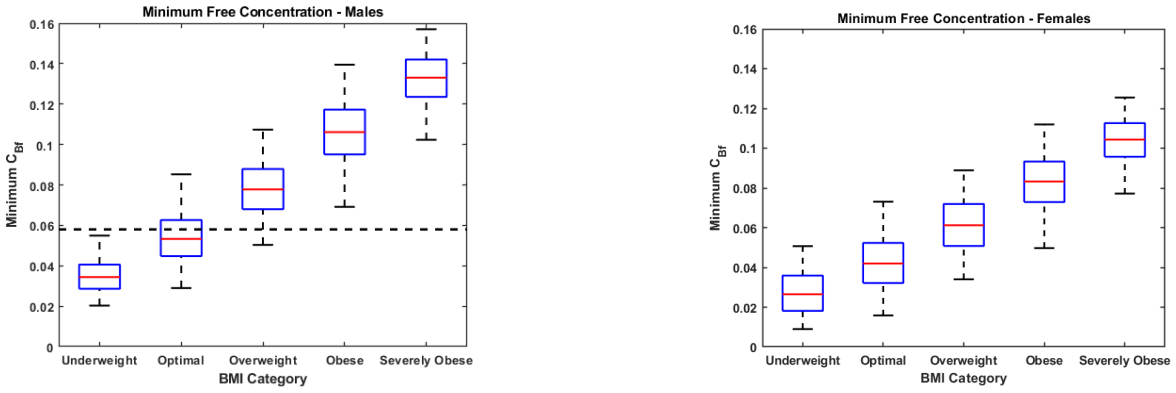


(a) Males **(b)** Females

Figure 7. Area under the Free Concentration Curve of Ertapenem in the Blood. Plot (a) illustrates the distribution of AUC for males; the dashed black horizontal line represents the AUC for the original normal height, normal weight male. Plot (b) illustrates the distribution of AUC for females.

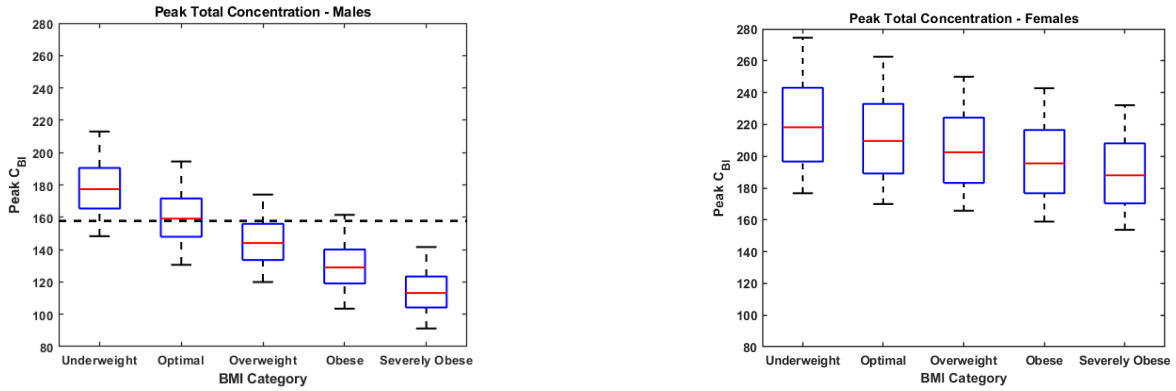
5. Discussion and conclusions

In this paper, we modified a previously developed PBPK model for a single gram dose of the antibiotic ertapenem administered intravenously. We examined the effects of sex and body mass index on the distribution and elimination of ertapenem in the body. From the model simulations, it appears that both BMI and sex may play significant roles in the distribution and elimination of ertapenem. In particular, females, most noticeably underweight females, have a higher area under the concentration



(a) Males **(b)** Females

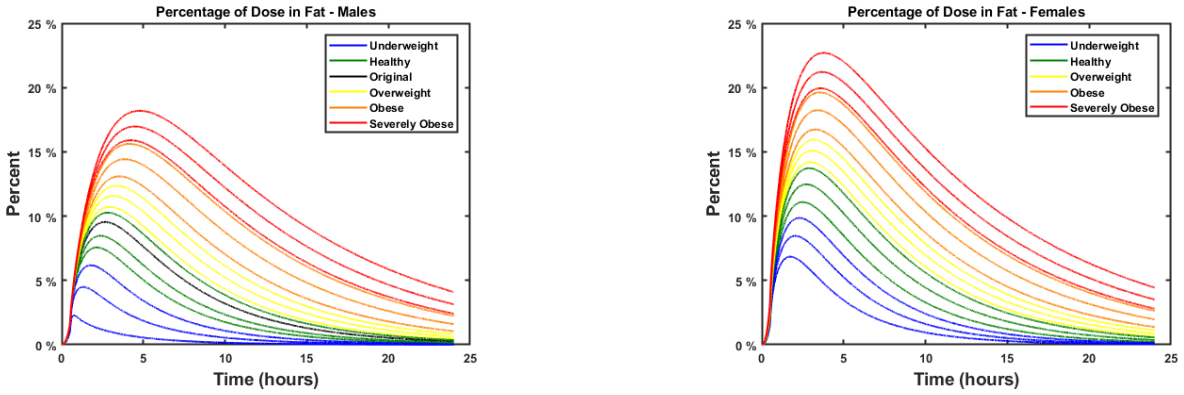
Figure 8. Minimum Free Concentration Curve of Ertapenem in the Blood. Plot (a) illustrates the distribution for males; the dashed black horizontal line represents the minimum free concentration for the original normal height, normal weight male. Plot (b) illustrates the distribution for females.



(a) Males **(b)** Females

Figure 9. Peak Total Concentration Curve of Ertapenem in the Blood. Plot (a) illustrates the distribution for males; the dashed black horizontal line represents the peak total concentration for the original normal height, normal weight male. Plot (b) illustrates the distribution for females.

curve and higher peak concentrations than males. This could potentially lead to more adverse side effects in females than those experienced in males. Moreover, the peak concentration increases in both males and females as the BMI decreases from severely obese down to underweight. Therefore, the peak concentration is expected to be higher for a lower BMI level in both males and females. This appears to at least be partially due to the percentage of the dose which is concentrated in the fat. The higher the BMI, the larger the percentage of the dose is expected to be in the fat and thus potentially not working to eliminate the bacteria as desired. Moreover, simulations indicate that underweight males and females eliminate the drug faster, thus having a lower minimum free concentration at the end of



(a) Males **(b)** Females

Figure 10. Percent of Dose of Ertapenem in the Fat. Plot (a) illustrates the percent for males; the solid black line represents the percent for the original normal height, normal weight male. Plot (b) illustrates the percent for females.

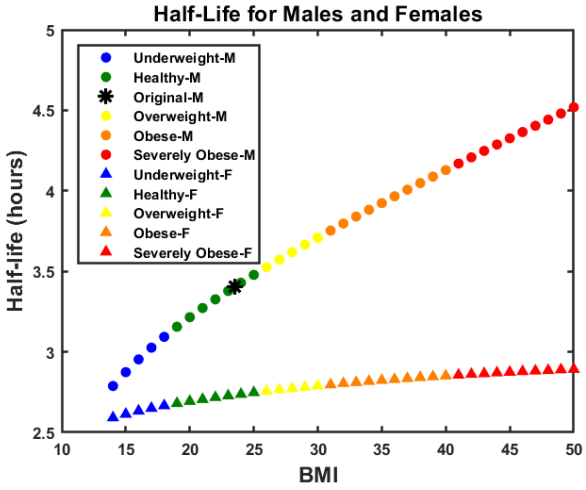


Figure 11. Half-life of ertapenem in males (M) and females (F) of different BMI classifications; the black star represents the half-life for the original normal height, normal weight male.

the dose. More research is needed to indicate whether or not this minimum concentration would fall below the minimum inhibitory concentration level for particular bacteria. Simulations also indicate that BMI does not greatly effect the half-life of the drug in females; however, the half-life for the drug in severely obese males is about twice as long as that indicated in underweight males.

Overall, in this article, we have shown using a PBPK model for ertapenem that the same dosage may not be optimal for all males and females given variation in BMI values. In future work, we hope to use the PBPK model for ertapenem for males and females of varying BMI to simulate what an optimal dose might be for a given individual according to a specified criteria for peak concentration, area under the concentration curve, half-life, and minimum inhibitory concentration for a particular bacteria.

Conflict of interest

The authors declare there is no conflict of interest.

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