Comparative Study of Parameter Estimation Methods in Pharmacokinetic Model with Oral Administration: Simulations of Theophylline Drug Concentration

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Abstract

Parameter estimation for the elimination and absorption rate constants is performed in a pharmacokinetic model, where a drug is administered orally. Some methods have been introduced to estimate these parameters but without comparison which one gives better estimates. Here, two different methods are used for comparison in estimating the absorption rate constant: the Wagner-Nelson and residual methods. The Wagner-Nelson method requiring fewer data sets while the residual method uses all available data sets for estimation. For the elimination rate constant estimate, we use only the least square error method. Simulations are conducted using sample data points of Theophylline drug concentration that varies over time to estimate the parameters. These parameter values are then utilized to approximate the drug concentration over time, using both methods. These approximations are then compared with the actual data sets to see and calculate the error values so that the best method can be determined. The comparison shows that the residual method provides better approximation since this method utilizes the entire sample data points, while the Wagner-Nelson uses only the data in the beginning time, that is when the absorption process is dominant.

Keywords: Pharmacokinetic Model, Parameter Estimation, Wagner-Nelson, Residual

Introduction

Pharmacokinetics is a study in the field of pharmacology that plays a crucial role in understanding the drug delivery process when drugs are administered into the body. The processes involved absorption, distribution, metabolism, and eventually the excretion of drugs out of the body. The last two processes can also be referred to elimination process. There are various routes of how drug is administered. The most very common routes are intravenous by injection or infusion and *per os* (*po*) or by mouth [7, 12]. When a drug is administered intravenously, the absorption process is omitted since the drug directly enters the bloodstream without undergoing absorption that takes place in the gastrointestinal tract (GIT).

The drug delivery process, starting from absorption until excretion, can be modeled in the form of mathematical equations, such as differential equations [8, 10] or fractional equations [2, 3, 14, 21] which indicating the rate of change in drug concentration in the body. With the pharmacokinetic

model, we can seek the solution so that we can observe any changes in drug concentration over time. On the other hand, we can also estimate parameters that appear in the model, such as the constant rates of absorption or elimination.

Many researchers have explored the drug delivery process in the body through mathematical models, as demonstrated by Savva [18, 19], who developed a model of differential equations to analyze the drug concentration dynamics in the plasma when intermittent infusion is taken. The dynamics can be observed by seeking analytical solutions to the model. Laplace transform can also be employed to see the drug concentration behavior, and this has been done by Khanday et al. [13], Rodrigo [17], and Reddy & Narayah [15]. When analytical solution is difficult to obtain, a numerical approach can be used, as demonstrated by Egbelowo [5, 6] and Al-Mumtazah [1], who utilized the nonstandard finite difference numerical method.

As mentioned above, in addition to seeking solutions of the mathematical model, pharmacokinetics also determines the estimation of parameters that appear in the model. The constant rates of drug absorption and elimination are the parameters that are commonly estimated [8, 20]. Least squares fitting [9] is the very familiar method used to estimate the elimination rate constant. On the other hand, Wagner & Nelson [22] has introduced the method to estimate the constant rate of absorption. Then comes the residual method [20] proposed as an alternative method for this estimation. These methods have lately been utilized by Zulkarnaen et al [24] to estimate parameters in the drug-drug interaction models when two drugs are administered orally and simultaneously.

In this article, we employ two methods: Wagner-Nelson and residual, to estimate parameters of the constant rates of absorption and elimination when the drug is administered orally. From these estimations, graphical simulations are established to illustrate the dynamics and changes in drug concentration over time. The results are then compared with the actual data set to assess the differences by calculating the root mean square error. By having the comparison, we will find out which method gives the best result known from the smallest root mean square error obtained.

Methods

In this paper, a mathematical model referred to [8, 12] is given. Once the model has been established, it is then solved in terms of the drug concentration that changes over time. Through this solution, two parameters that appear in the model are estimated. First the constant of elimination rate using the least square error method followed by the constant of absorption rate using two different methods: the Wagner-Nelson and residual methods. To estimate these parameters, data points of drug concentration that changes over time are needed which are obtained from [23]. Once the parameter estimates have been achieved from the two different methods, the solution can be established to calculate the root mean square error. Through this calculation of errors, we can make a conclusion to see which method is better.

Now we begin with a mathematical model which describes the rate of change of drug concentration in blood plasma, expressed as

$$\frac{dX}{dt} = k_a X_a - kX, \quad X(0) = 0. \tag{1}$$

This is a typical and common model used for oral drug administration. The notation $X = X(t)$ represents the amount of drug in the plasma that varies over time, while k_a and k respectively denote the absorption and elimination rate constants of the drug, where $k_a > k$. The value $X(0) = 0$ signifies that there is no drug in the plasma initially since it has not yet entered the bloodstream. In

other words, the drug is still in the GIT before being absorbed into the bloodstream. Therefore, the dynamics of the drug in the GIT needs to be observed first by using the model

$$\frac{dX_a}{dt} = -k_a X_a, \quad X_a(0) = X_0,$$

where X_a represents the amount of the drug in the GIT. By applying the separation of variables method (this method can be studied in [4, 13]), we obtain the solution of the amount of drug in the GIT as

$$X_a = X_0 e^{-k_a t}. \tag{2}$$

This solution is then inserted into (1) so that it can be further written as

$$\frac{dX}{dt} = k_a X_0 e^{-k_a t} - kX. \tag{3}$$

Employing the integrating factor, the solution of the amount of the drug in the bloodstream is obtained as

$$X(t) = \frac{k_a X_0}{k_a - k}\left(e^{-kt} - e^{-k_a t}\right).$$

It should be noted that $X = CV$, where C is the drug concentration in the bloodstream, and V is the volume of drug distribution. Therefore, the solution of the drug amount from the latter equation can be converted into the drug concentration as

$$C(t) = \frac{k_a X_0}{V(k_a - k)} e^{-kt} - \frac{k_a X_0}{V(k_a - k)} e^{-k_a t}. \tag{4}$$

Next, from this equation, we seek formulas to estimate the elimination rate constant k as well as the absorption rate constant k_a. This can be done subsequently by estimating k first, followed by k_a. To estimate k, we use only the data of concentration with large time, while for ka we can use either the data for small time or the entire time, depending on the method we use.

The first parameter to be estimated is the elimination rate constant k, where only the large time is used, say $\hat{t}$. This means we can assume that the absorption process has been completed, and the drug has been fully absorbed into the blood, or the absorption is still ongoing but is dominated by the elimination. Thus, we can call this time phase as elimination phase, and we can mathematically state that $e^{-k_a t} \approx 0$ since $\hat{t}$ is large and $k_a > k$. As a result, equation (4) can be simplified to

$$C_e(\hat{t}) = \frac{k_a X_0}{V(k_a - k)} e^{-k\hat{t}}. \tag{5}$$

By linearizing this equation, we obtain

$$\ln C_e(\hat{t}) = -k\hat{t} + \ln\left(\frac{k_a X_0}{V(k_a - k)}\right).$$

The purpose of this linearization is to enable the application of the least squares fitting. According to [9], we can derive formulas from the linear equation to calculate the slope and the y-intercept. As a result, from the latter equation we can calculate the parameters k and k_a as

$$k = -\frac{m_1 \sum_{i=1}^{m_1} \hat{t}_i \ln C_{e,i} - \sum_{i=1}^{m_1} \hat{t}_i \sum_{i=1}^{m_1} \ln C_{e,i}}{m_1 \sum_{i=1}^{m_1} \hat{t}_i{}^2 - \left(\sum_{i=1}^{m_1} \hat{t}_i\right)^2}, \tag{6}$$

and

$$\frac{k_a X_0}{V(k_a - k)} = \exp\left(\frac{\sum_{i=1}^{m_1} \hat{t}_i{}^2 \sum_{i=1}^{m_1} \ln C_{e,i} - \sum_{i=1}^{m_1} \hat{t}_i \ln C_{e,i} \sum_{i=1}^{m_1} \hat{t}_i}{m_1 \sum_{i=1}^{m_1} \hat{t}_i{}^2 - \left(\sum_{i=1}^{m_1} \hat{t}_i\right)^2}\right), \tag{7}$$

where m_1 is the number of data points used for estimation, that is as the same size as $\hat{t}$.

Next, we estimate the second parameter, namely the absorption rate constant k_a. In this article, two different methods are utilized for this estimation. The first method is the Wagner-Nelson method, introduced for the first time in 1964 [22], and the second method is the residual method

introduced later [8, 16]. The use of these methods aims to convey which method provides a better estimate by performing simulations that will be demonstrated in the later section.

A. Wagner-Nelson Method

In this method, only some data points are used to estimate the absorption rate constant, which are the data points at small time, where the absorption dominates the elimination process. Let we denote the time by $\tilde{t}$. The first step taken by Wagner and Nelson to estimate the absorption rate constant is by defining the fraction of the absorbed drug into the bloodstream, denoted by X_b as

$$\frac{X_b}{X_b^\infty} = \frac{C+k[AUC]_0^{\tilde{t}}}{k[AUC]_0^\infty}.$$

Therefore, we can write that the fraction of the unabsorbed drug as

$$1 - \frac{X_b}{X_b^\infty} = 1 - \frac{C+k[AUC]_0^{\tilde{t}}}{k[AUC]_0^\infty}, \tag{8}$$

where $[AUC]_0^{\tilde{t}} = \int_0^{\tilde{t}} C(t)\, dt$ representing the area under curve of the drug concentration. On the other hand, to determine the amount of the remaining (unabsorbed) drug in the GIT, we can also refer to equation (2) by rewriting

$$\frac{X_a}{X_0} = e^{-k_a \tilde{t}}. \tag{9}$$

Here, X_a/X_0 represents the fraction of the drug that still present in the GIT, which also means the fraction of the drug that is not absorbed. Therefore, by comparing equations (8) and (9), we can conclude that

$$1 - \frac{C+k[AUC]_0^{\tilde{t}}}{k[AUC]_0^\infty} = e^{-k_a \tilde{t}}.$$

From here we have the linearized equation

$$\ln\left(1 - \frac{C+k[AUC]_0^{\tilde{t}}}{k[AUC]_0^\infty}\right) = -k_a \tilde{t},$$

so that the least squares fitting can be implemented to calculate the absorption rate constant as

$$k_a = -\frac{m_2 \sum_{i=1}^{m_2} \tilde{t}_i \ln C_{ab,i} - \sum_{i=1}^{m_1} \hat{t}_i \sum_{i=1}^{m_1} \ln C_{ab,i}}{m_2 \sum_{i=1}^{m_1} \tilde{t}_i{}^2 - \left(\sum_{i=1}^{m_1} \tilde{t}_i\right)^2}, \tag{10}$$

where $C_{ab,i} = 1 - \left(C + k[AUC]_0^{\tilde{t}_i}\right)/(k[AUC]_0^\infty)$ for $i = 1 \ldots m_2$, and m_2 denotes the number of data sets used for k_a estimation.

B. Residual Method

Unlike the Wagner-Nelson method, which uses only a small-time data set to estimate the absorption rate constant, the residual method utilizes all data points. The first step in this method is to extend the drug concentration values from the elimination phase back to the very beginning phase, so now the drug concentration given in (1) can be calculated to the entire time. In other words, the concentration values are not only applicable for large time values only but also for all times, including $t < \hat{t}$.

The C_e values in (1), which are now known for all time using (2) and (3), are compared with their original concentration values, denoted by *C* given in (4). The comparison involves finding the differences between these two concentration values by subtracting equations (4) by (5), and the result is referred to as the residual value *R(t)*. Thus, we can write

$$R(t) = C(t) - C_e(t) = \frac{k_a X_0}{V(k_a - k)} e^{-k_a t}.$$

Like in the elimination phase, here we also perform linearization to the residual function, so it becomes

$$\ln R(t) = -k_a t + \ln\left(\frac{k_a X_0}{V(k_a - k)}\right).$$

We can eventually calculate k_a based on the slope of the linear equation with the formula

$$k_a = -\frac{n\sum_{i=1}^{n} t_i \ln R_i - \sum_{i=1}^{n} t_i \sum_{i=1}^{n} \ln R_i}{n\sum_{i=1}^{n} {t_i}^2 - \left(\sum_{i=1}^{n} t_i\right)^2}. \quad (11)$$

Here *n* is the number of the entire available data points used for k_a estimation.

Results and Discussion

In this section, some simulations are conducted to demonstrate the implementation of the formulas obtained to estimate parameters of the elimination and absorption rate constants. The required data for the estimation consists of a set of drug concentration samples over time. In this context, we utilize Theophylline drug sample data points gathered from [23] and shown by Table 1. It can be observed from the table that the drug concentration increases initially, and this occurs due to the dominant absorption process compared to the elimination, then reaching a peak close to 12.9 μg/ml, and finally decreases as the effect of the completion of the absorption process, only elimination process continues until the drug is completely removed from the body.

Table 1. Data set of time versus drug concentration of Theophylline.

t (hour)	0	0.5	1	2	3	4	5
C(t) (μg/ml)	0	2.2	3.3	4.6	7.7	8.5	10.9
t (hour)	6	8	10	12	14	16	20
C(t) (μg/ml)	11.8	12.9	10.9	10.7	8.2	7.1	5.1

From the data we have, we first use the data only for the time that is considered large to estimate the elimination rate constant by referring to the formula given in (6). Here, we take the last seven data points, assuming that these data points represent the phase when the elimination is much more dominant than the absorption process, or it can be considered that the absorption process has been completed at this phase. As a result, we have the estimated elimination rate constant value as *k* = 0.0656/hour.

Next, we estimate the absorption rate constant k_a. As explained earlier, two different methods are employed to estimate this parameter. For the Wagner-Nelson method, the estimation is performed using the formula given in (10). It should be noted that this method utilizes data when the absorption process is considered dominant compared to the elimination. Therefore, we choose the first three data sets from the data in Table 1, and the result, we yield the value k_a = 0.3670/hour. On the other hand, the residual method produces the estimation of $k_a = 0.2955$/hour by calculating (11) using all the available 14 data points.

As the estimates for the parameters *k* and k_a have been done, as well as the supporting parameter calculated by (7) that results 20.44 μg/ml, further we need to compare which one among the two methods provides the best estimation. To answer this, the root mean squares error (RMSE), formulated by

$$\text{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(\hat{C}_i - C)},$$

is used here to calculate the error between the concentration values of the estimated values and the actual concentrations. denoted by $\hat{C}$ and C, respectively. The RMSE values along with the estimate parameter values obtained from the two methods are summarized in Table 2 for ease of comparison.

Table 2. The estimation values along with the root mean squares error.

Method	K	k_a	RMSE
Wagner-Nelson	0.0656	0.3670	1.5726
Residual	0.0656	0.2955	0.3033

From the table, we can see that both methods produce $k_a > k$, which aligns with the assumption we have previously stated. Furthermore, when we observe and compare both RMSE values, the residual method yields an error which is five times smaller than the error produced when the Wagner-Nelson method is used.

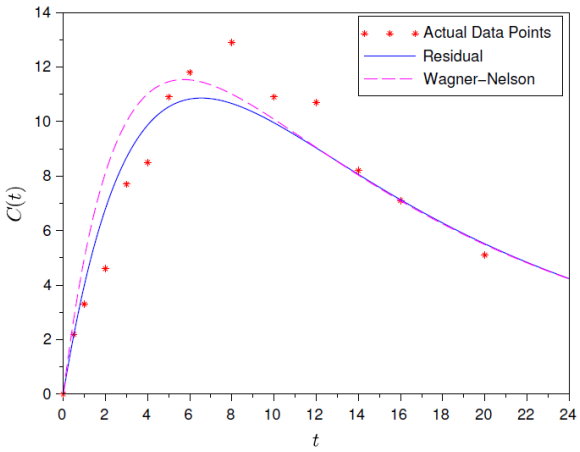


Figure 1. Graphs of the approximations of the drug concentration with the actual data points.

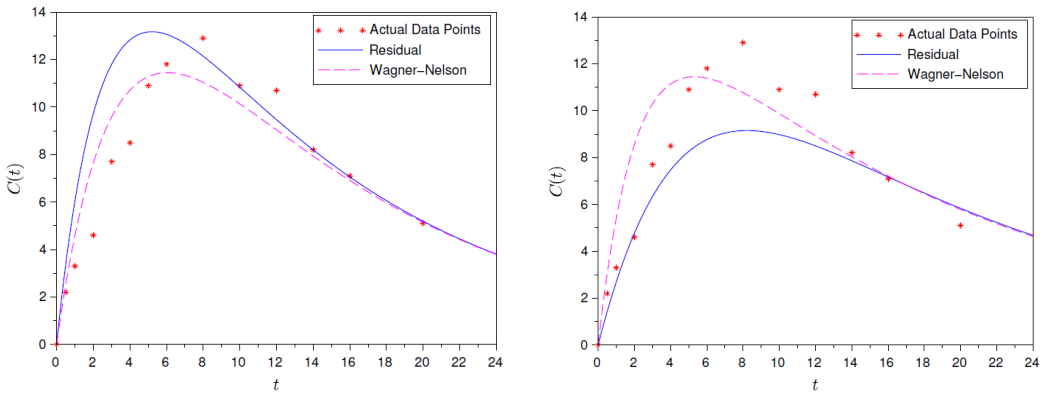
Now, the number of data used for k estimation is varied to see the effect of the RMSE values. Table 2 presents the RMSE results of three simulations of estimation with three different number of sample data points. For convenience, we put the simulation for 7 data points that has been performed and shown in Table 2 into Table 1. Now when we reduce the number of data points from 7 to the last 6 data points, the residual method produces a higher RMSE value which is in line with the Wagner-Nelson method. However, the residual method shows a larger increase in error, specifically five times higher, while the Wagner-Nelson method has only 15% increase.

Conversely, when the data is increased to the last 8 data points, the residual method provides an approximation that is quite distant from the actual data, especially when the elimination process begins to dominate over the absorption process. In contrast, the Wagner-Nelson method provides a better approximation, especially as the time for the elimination process becomes dominant. Graphical simulations based on Table 2 are shown in Figure 2.

Table 3. Comparisons of the RMSE values for the varying number of data points used for estimation.

Method	RMSE		
	6 data	7 data	8 data
Wagner-Nelson	1.7760	1.5726	1.3773
Residual	1.5985	0.3033	2.3766

Observe that in the graphical simulation for 6 data points shown in Figure 2a, the Wagner-Nelson method initially provides a better estimate when the absorption process is still dominant. However, this situation reverses when the elimination process becomes dominant. On the other hand, the residual method shows better estimation for the elimination-dominant phase than in the beginning phase.



(a) (b)

Figure 2. Graph comparisons between (a) the reduced and (b) the increased number of data points.

For the second scenario, that is when the data is increased to 8 data points, the residual method provides approximation that is quite distant from the actual data, especially as the elimination process begins to dominate over the absorption process. In contrast, the Wagner-Nelson method provides a better approximation, especially when the elimination process is dominant. It should be noted that the comparison results may be different when a different drug (other than Theophylline) is implemented.

Conclusion

Parameter estimates for elimination and absorption rate constants have been conducted in this paper. Two methods were employed as tools for estimation: Wagner-Nelson and residual. For Wagner-Nelson, only a small number of data is needed to calculate the absorption rate constant, specifically data from the initial phase when the absorption process is more dominant than the elimination phase. In contrast, the residual method utilizes data of the entire phase. As a result, the residual method gave better approximation compared to the Wagner-Nelson because it utilizes more information gathered from the entire sample data points.

When the number of data sets used to estimate the elimination rate constant were varied, the residual method yielded an inconsistent result, and it was very sensitive to this variation. Consequently, the RMSE values increased five to seven times larger. However, this does not apply to the Wagner-Nelson method, which was relatively consistent and not sensitive to the changes in the number of data for estimation. With an increasing number of data points for estimation, the RMSE becomes smaller, even though not as small as the residual method when using seven data points.

Based on the statements above and the simulations performed, the residual method can be considered as the better method than the Wagner-Nelson method for estimating parameters when a drug is administered orally, provided the number of data set used to estimate the elimination rate constant must be chosen right. If not, the Wagner-Nelson method may provide better results.

Acknowledgments

The authors would like to thank Mathematics department of UIN Sunan Gunung Djati Bandung for funding this publication.

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