A Comparison of Minimal Pharmacokinetic Models for an Anti-diabetic Agent

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Abstract

In diabetes studies, pharmacologists rely on statistical techniques tied with experimental results to describe the plasma concentration of an anti-diabetic agent. However, these sets of statistical information only provide minimal inference to the drug's kinetics. To understand the effect of an anti-diabetic agent to a glucose-insulin system, it is necessary to predict its movement in the system over a specific time interval. In this study, a set of simple pharmacokinetic models was formulated to describe the dynamics of the plasma concentration of an anti-diabetic agent known as metformin. The models were fitted to empirical data via nonlinear regression analysis and were compared using Akaike information criterion to determine the most reasonable model and parameter estimates. The results reveal that models considering varying absorption rate have a promising fit. These models can be extended to multiple drug dosage cases and can be used to estimate rate constants associated to other anti-diabetic agents.

Keywords: pharmacokinetic models, modelling diabetes, metformin, regression analysis, Akaike information criterion, parameter estimation, glucose-insulin system

Pharmacokinetics is a study of how the plasma concentration of the drug changes within the body, which entails the time course of its absorption, distribution, metabolism, and excretion. Since drug movement is a complex process and so difficult to predict, the development of pharmacokinetic models is necessary (Landersdorfer and Jusko, 2008). A basic type of model used in pharmacokinetics is the compartmental model where the compartments represent a group of similar tissues or fluids.

In diabetes studies, a compartmental modelling approach has been used to understand the dynamics of the disease especially within the framework of glucose-insulin system (Topp et al, 2000). Though models of sufficient simplicity, i.e. minimal models, describing the observed glucose-insulin dynamics have been developed as starters and have been extended to include other factors such as effect of drug use, the dynamics of the plasma concentration of an anti-diabetic agent are not clearly understood. For instance, an anti-diabetic agent such as *metformin* is known to exhibit glucose-lowering effect by decreasing hepatic glucose production, reducing the rate of intestinal glucose absorption, and increasing glucose uptake by peripheral tissues (Stepensky et al, 2000), yet the plasma concentration of metformin is partially investigated (Lee and Kwon, 2004).

The primary aim of this study is to formulate simple pharmacokinetic models describing the dynamics of the plasma concentration of an anti-diabetic agent, such as metformin, and compare these models to empirical data. Three models, in the form of ordinary differential equations (ODEs), are developed here with progressing complexity. The solutions of these ODE models are obtained analytically and used for curve fitting. Parameter estimates are obtained using nonlinear regression analysis. The performances of these models are compared in terms of how well they fit the empirical data using Akaike information criterion (AIC) (Akaike, 2011) since it is assumed that the candidate models are only approximations to the observed metformin plasma concentration and AIC does not consider that any of the candidate models

being tested is the true model.

The minimal models developed in this study can be used for diagnostic purposes in describing the effect of drugs. This study also serves as a guide to identify a reasonable model to begin with in developing new pharmacokinetic models for other anti-diabetic agents. Furthermore, the models can be extended to incorporate other factors affecting the dynamics of plasma concentration of an anti-diabetic agent.

Materials and Methods

Model description

To begin, let $c(t)$ be the plasma concentration of metformin in micrograms per milliliter (mg/ml) at time *t* hours. In a well-mixed system, the rate of change in the plasma concentration of metformin over time is governed by its rates of absorption and clearance in the blood and is specifically given by

$$\begin{pmatrix} \text{Rate of change} \\ \text{in plasma concentration} \\ \text{of metformin} \end{pmatrix} = \begin{pmatrix} \text{Absorption} \\ \text{rate} \end{pmatrix} - \begin{pmatrix} \text{Clearance} \\ \text{rate} \end{pmatrix} \quad (1)$$

Using this formula, three models are derived based on the assumptions made about the absorption rate of the drug in the blood. For simplicity, all models take the assumption that the clearance rate varies linearly with the plasma concentration of metformin, where the clearance rate constant is denoted by *d*.

One of the challenges in developing the model equations associated to equation (1) is the construction of functional form for the absorption rate. Since a general functional form of the absorption rate is not known, the models must be formulated according to crude assumptions that have not been tested experimentally. As first step, a simplistic view of the absorption rate is considered wherein the orally administered drug is assumed to be absorbed within the system at a constant rate α for τ hours ($\tau < \tau_0$), where τ_0 is the time period to observe the plasma concentration dynamics of the drug. Beyond τ hours up to time τ_0, the drug has been fully absorbed and so its dynamics is only driven by its clearance rate. This mechanism implies that the absorption rate behaves in a switch-like manner whose functional form can be represented as a step function. Hence, the ODE for the first model, i.e. Model 1, is

$$\frac{dc}{dt} = \begin{cases} \alpha - \delta c, & 0 \le t \le \tau \\ -\delta c, & \tau \le t \le \tau_0 \end{cases}, \quad (2)$$

with initial plasma concentration $c(0) = 0$.

As the first model is built on an assumption that the absorption rate is a switch-like function, it can be thought that the system does not necessarily respond this way. One way to modify Model 1 is by assuming that the absorbed drugs decrease exponentially over time $(0 \le t \le \tau_0)$ instead of putting a time limit at which the system ceases to absorb the drug. This point means that the absorption rate is assumed to be an exponentially decaying function – an assumption used to formulate the model equations for the second model. To model the absorption rate as an exponential decay, let $a(t)$ be the absorbed drug over *t* hours. Suppose that *k* is the decay rate for $a(t)$, then the ODEs for the second model (Model 2) are given by

$$\begin{cases} \frac{da}{dt} = -ka \\ \frac{dc}{dt} = ka - \delta c \end{cases}, \quad (3)$$

where the initial value $a(0) = a_0 > 0$.

Finally, one can impose a more dynamic absorption rate by assuming that drugs absorbed build up at a rate $\alpha - ka$ over time $\tau \le \tau_0$ then decay exponentially beyond τ. Mathematically, it can be seen that $a(t)$ resembles the delta function. This assumption yields Model 3 whose equations are given by

$$\begin{aligned} \frac{da}{dt} &= \begin{cases} \alpha - ka, & 0 \le t \le \tau \\ -ka, & t \ge \tau \end{cases}, \\ \frac{dc}{dt} &= ka - \delta c, \end{aligned} \quad (4)$$

and $a(0) = 0$, i.e. no drugs are absorbed initially.

In terms of model structure, Model 3 is clearly an augmented form of Model 2. Specifical-

ly, the dynamic variable $a(t)$ in Model 3 is modelled as piecewise ODEs, i.e. additional level of complexity, while $a(t)$ in Model 2 is just a simple ODE. In contrast with Model 1, Models 2 and 3 have dynamic absorption rates. The third model is the most complex among the rest and includes more parameters to be estimated, which has a consequence in model ranking.

Parameter estimation and nonlinear regression analysis

Models 1 to 3, i.e. equations (2)-(4), display a set of parameters whose values are not known. For parameter estimation, the data points depicting the mean observed values (22 human subjects) of plasma concentration of metformin (500 *mg* oral administration) from an experimental study (Lee and Kwon, 20014) were extracted using a *Java*-written program (Tummers, 2006) (see Table 1).

Since the model parameters and dynamic variables are related in a nonlinear fashion, each model is fitted to the experimental data using a least squares method (i.e. nonlinear regression analysis) (Bates and Watts, 1988). This procedure was implemented in MATLAB, a computer software with curve fitting functionality.

Akaike information criteria (AIC)

The Akaike information criterion (AIC) is a technique that evaluates which of the models being compared performs best relative to each other according to the measurements of their goodness-of-fit. Generally, the *AIC* is computed using the formula:

$$AIC = 2k - 2\ln(L) \tag{5}$$

where k is the number of model parameters and L is the maximum likelihood for the estimated model[8]. As a rule, the best model yields the minimum *AIC*. Practically, the relative probability that the ith model minimizes the information loss is used, which is given by the expression

$$\exp\left(\left(AIC_{\min} - AIC_i\right)/2\right) \tag{6}$$

where $AIC_{\min}$ is the minimum *AIC* value among the *AICs* of the candidate models. If this probability is very small, then it implies that the ith model most likely loses information and so must be omitted (Burnham and Anderson, 2003). In this study, the AIC_c is used because of small sample size. For small data points, n, or large k, AIC_c is strongly recommended (Burnham and Anderson, 2003). In fact, AIC_c converges to *AIC* as n increases. Given a computed *AIC* using (1), the corrected AIC is given by

$$AIC_c = AIC + \frac{2k(k+1)}{n-k-1} \tag{7}$$

To apply least squares model fitting, it is assumed here that the residuals associated to the candidate models are normally distributed, i.e. the variance in the likelihood function are identical. As a consequence of this assumption, alternative form for *AIC* is used to substitute in (7). Here *AIC* is computed as

$$AIC = n\ln\left(RSS/n\right) + 2k, \tag{8}$$

where *RSS* is the residual sum of squares (Burnham and Anderson, 2003) whose formula is given by

$$RSS = \sum_{i=1}^{n}\left(y_i - f\left(x_i\right)\right)^2. \tag{9}$$

In this study, y_i represents the observed values for the plasma concentration of metformin and $f\left(x_i\right)$ is the metformin plasma concentration at

Table 1: Data of metformin plasma concentration over a time-period of 12 hours extracted from Lee and Kwon (2004).

Time (hours)	Plasma concentration of metformin (μg/mL)
0.5	0.45
1.0	0.90
1.5	1.08
2.0	1.13
2.5	1.14
3.0	1.20
4.0	1.11
6.0	0.62
8.0	0.37
10.0	0.22
12.0	0.12

time x_i hours predicted by the different models.

Results and Discussion

The analytic solutions of aforementioned ODE models were obtained using elementary techniques for solving first-order differential equations, e.g. separation of variables or by the method of integrating factors (Nagle et al, 1989), and are displayed in Table 2. The method of Laplace Transform can also be used to compute these analytic solutions. In Table 2, it can be noticed that $\tau_0 = 12$, which was essentially derived from the observed amount of metformin plasma concentration for only one cycle in a period of 12 hours, is also shown in Table 1.

The analytic form of each model was used in nonlinear regression analysis with the data presented in Table 1. The analysis yielded parameter estimates for each model as well as the corresponding RSS. To compute the corrected *AIC* of each model using (7), the RSS associated to each model was substituted to (8). The estimated parameters and computed AIC_c of each model is summarized in Table 2.

As seen in Table 2, the analytic solution of Model 1 is a linear combination of a constant and an exponential decay with rate δ, i.e. clearance rate, from 0 to 1.83 hours, which implies that metformin plasma concentration increases during this time duration. On the other hand, for time between 1.83 and 12 hours, the analytic solution of Model 1 depends on the term $e^{-\delta t}$ and so it is expected that the metformin plasma concentration decreases exponentially over this period. Moreover, it is noteworthy to mention that the left- and right-hand first derivatives of $c(t)$ at τ are not equal. Hence, the graph of $c(t)$ predicted by Model 1 must show a sharp peak at τ, which is indeed the case

Table 2. The different analytic forms of metformin plasma concentration based on (2)-(4), their parameter estimates, and calculated AIC_c using (7)-(8).

Model	Analytic Solution, $c(t)$	Parameter estimates[a]	AIC_c value
1	$c(t)=\begin{cases}\frac{\alpha}{\delta}\left(1-e^{-\delta t}\right), & 0\le t<\tau\\ \frac{\alpha}{\delta}e^{-\delta t}\left(e^{\delta\tau}-1\right), & \tau\le t<12\end{cases}$	$\alpha=0.8690$ $\delta=0.1877$ $\tau=1.8316$	-46.00
2	$c(t)=\frac{ka_0}{\delta-k}\left(e^{-kt}-e^{-\delta t}\right)$	$\delta=4.0648\times10^{-1}$ $a_0=3.2028$ $k=4.0652\times10^{-1}$	-64.60
3	$c(t)=\begin{cases}\frac{\alpha}{\delta}-\frac{\alpha}{\delta-k}e^{-kt}+\left(\frac{\alpha}{\delta-k}-\frac{\alpha}{\delta}\right)e^{-\delta t}, & 0\le t<\tau\\ \frac{\alpha}{\delta-k}\left(e^{k\tau}-1\right)e^{-kt}+\left(\frac{\alpha}{\delta}-\frac{\alpha}{\delta-k}\right)\left(e^{\delta\tau}-1\right)e^{-\delta t}, & t\ge\tau\end{cases}$	$\alpha=14.55$ $\delta=424.7836\times10^{-3}$ $k=424.7814\times10^{-3}$ $\tau=0.2243$	-64.58

[a] The units are given as follows: $\mu g\ ml^{-1}h^{-1}$ for α, $\mu g\ ml^{-1}$ for a_0, h^{-1} for δ and k, and h for τ. Note that *h* here stands for hour.

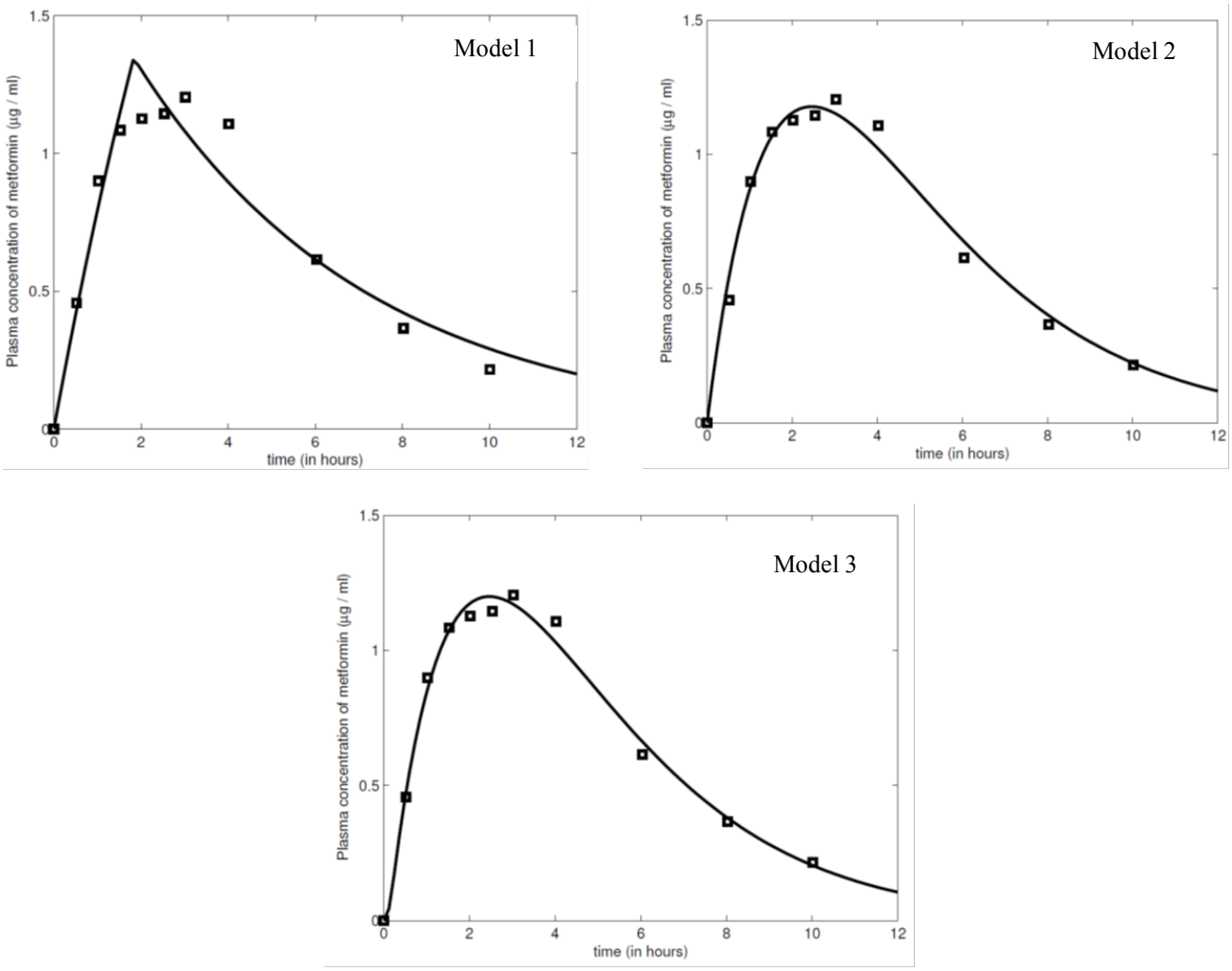

Figure 1. The best fit curves (solid curves) of Models 1-3 and 11 data points (open squares) representing mean observed values of metformin plasma concentration after oral administration of 500 mg tablet within 12 hours.

as found in Figure 1.

In contrast with Model 1, the analytic solution of Model 2 is a linear combination of two different exponentially decaying functions namely e^{-kt} and $e^{-\delta t}$. Note that the metformin plasma concentration $c(t)$ predicted by Model 2 is not a piecewise function. However, Model 2 analytic solution depends on the difference between e^{-kt} and $e^{-\delta t}$ with slightly different decay rates ($\delta > k$), which is not monotonic. As a matter of fact, setting the first derivative of $c(t)$ to zero

$$t = \frac{1}{\delta - k} \ln\left(\frac{\delta}{k}\right) \approx 2.46$$

yields hours, and by the second derivative test, it is concluded that this is the time when $c(t)$ is at maximum. Models 1 and 2 have the same number of parameters to be estimated, implying that the difference in their AIC_c values is due to their differences in the RSS values. One can see from the AIC_c values that the RSS associated to Model 1 must be larger than that of Model 2. Therefore, Model 2 performs better than Model 1 in predicting $c(t)$ with the given data set.

The analytic solution of Model 3 as dis-

played in Table 2 is also a linear combination of the functions e^{-kt} and $e^{-\delta t}$ as in Model 2. However, it takes a more complicated form. Specifically, the $c(t)$ in Model 3 is defined as a piecewise function and the coefficients of the exponential functions are long rational expressions in terms of all model parameters. Moreover, Model 3 has very small estimated values for the decay rates k and δ, which mainly differs with those estimated decay rates in Model 2. Furthermore, Model 3 has more parameters to estimate than the other models. As shown in Figure 1, the graph of $c(t)$ predicted by Model 3 resembles that of Model 2, which is equivalent to stating that their RSS values are close to each other. Hence, it is not surprising that AIC_c values of Models 2 and 3 are very close to each other and the slight discrepancy can be explained by their differences in the number of parameters.

Figure 1 show plots of the data and the best fit curves for plasma concentration of metformin over time. The data points are depicted in open squares and the solid curve is the analytic model substituted with the estimated parameters. The figure shows three panels corresponding to the least squares fitting of Model 1 (top panel), Model 2 (middle panel), and Model 3 (bottom panel).

The relative likelihood of each model can be computed using (6) with $AIC_{\min} = -64.6$, i.e. the *AIC* for Model 2. Although it may be straightforward to see that Model 1 is not a good model from Figure 1, the relative likelihood computation additionally supports this claim. In particular, the AIC_c value of Model 1 can be substituted to (6) to obtain $\exp\left(\left(-64.6+46\right)/2\right) \approx 9.14\times10^{-5}$, the relative likelihood of Model 1. This computed value means that Model 1 has a very small relative probability (about 10^{-5}) of minimizing information loss and so can be neglected when deciding for good models to use in describing the pharmacokinetics dynamics of metformin.

Conclusion

Among the three formulated simple pharmacokinetic models, the best fitted model is Model 2, which takes into consideration a (decaying) exponential rate of absorption for the drug. The model consists of three parameters to be estimated, namely, the initial absorption rate, the decay rate of absorption, and the clearance rate, which can be used for further analysis, for instance, extending the model for multiple dosage cases or including the model to see its effect in a glucose-insulin model for diabetes.

Now that a best fit yet a simple model for the plasma concentration of metformin is known, this study proposes that the same model should be fit to see if the dynamics of other anti-diabetic agents is comparable with that of metformin. Anti-diabetic agents, such as glimepiride (Niemi et al, 2000), gliclazide (Park et al, 2003), repaglinide (Hatorp, 1999), etc., have known plasma concentration profile and by applying the same method of comparison that was demonstrated here, it is possible to obtain a different set of estimated parameters. Subsequently, a comparison between anti-diabetic agents in terms of their pharmacokinetic dynamics become feasible.

Finally, it is possible for these three models to yield different sets of *AIC* values when fitted to temporal data of plasma concentration for other anti-diabetic agents leading to changes in model preference. This study sets the stage to answer questions such as: which pharmacokinetic model is appropriate for this anti-diabetic agent? The researcher can use the method of analysis and comparison presented here as first steps in addressing such a question.

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