Pharmacokinetics simulation of Metformin in type 2 Diabetes Mellitus

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Abstract. The aim of this study was to explore the pharmacokinetic relationship of metformin on glucose levels after the administration of metformin in type 2 diabetes mellitus. The pharmacokinetics of metformin was assessed using intravenous glucose tolerance tests before and after metformin administration. Type 2 diabetes mellitus is a metabolic disturbance which is caused by the pancreas that cannot produce enough insulin or body cannot use insulin which is produced effectively (low insulin sensitivity). Therefore, there is glucose level concentration escalation inside blood, where blood glucose level is more than normal level or known as hyperglycemia. Type 2 diabetes mellitus signed by muscle resistance and tissue to insulin, the decrement of insulin produced in the pancreas, and glucose absorption in the liver. Giving metformin to type 2 diabetes mellitus subjects increased glucose absorption in periphery tissue and liver but it did not impact insulin because metformin worked similarly to insulin and it did not impact beta cell function, so after or before metformin given, insulin concentration would not change, the effect of decrement of glucose following the concept of decay.

1. Introduction

A disease that causes glucose-insulin endocrine metabolic disorder in the human body, in which the pancreas either does not release insulin or insufficient insulin production in beta-cells, and also the tissue resistance against secreted insulin, so it leads to excessive blood glucose concentration level, this disease commonly is called type 2 diabetes mellitus (T2DM). Insulin will be produced by beta-cells in the pancreas and can work to lower blood glucose concentration back down to within the normal range of human body when blood glucose concentration level rises too high after the human body is administrated a glucose meal. To maintain glucose concentration level in a narrow range 70-110 mg/dl, the pancreas in the human body always release insulin. If the glucose concentration level in the human body is significantly out of the normal range, this human body is considered to have the blood glucose concentration problem, it will be hyperglycemia (>110 mg/dl) or hypoglycemia (<70 mg/dl).

In T2DM subjects, insulin can be produced normally by beta-cells in the pancreas, however, the cells in their bodies cannot use the insulin properly, due to the cells in their bodies have become resistant to insulin entirely. Its make to highly elevated blood glucose concentration level, this condition called hyperglycemia. As a result of this condition, T2DM subjects need to take anti-hyperglycemic drugs to maintain their blood glucose concentration level within a normal range [1, 2].

One choice of anti-hyperglycemic drugs for T2DM subjects is metformin (dimethyl biguanide). Metformin is widely used in the treatment of T2DM or non-insulin dependent diabetes mellitus (NIDDM). Over forty years, metformin has been used as an effective anti-hyperglycemic drug for T2DM subjects. To lower blood glucose concentration level, metformin will work to decrease glucose absorption in the intestinal, decrease hepatic glucose output, and increase the rate of absorption of glucose in the muscle cells and fat tissue. In most therapies of T2DM, a 500 mg or 850 mg doses of metformin is usually administered intravenously. Due to in the fact that metformin cannot completely be absorbed in the intestine, then metformin will not be metabolized, so it can be eliminated through the urinary system [3-5].
Pharmacokinetics is the study of the absorption, distribution, metabolism, and elimination of drugs in different body fluids and tissues. This study allows developing a mathematical model that can describe the complex dynamic processes relationships such as absorption, distribution, metabolism, and elimination of the drugs. The pharmacokinetic processes can also determine the drug concentrations in various tissues of the human body. This pharmacokinetic analysis of the drugs can aid to decide the correct dosage of the drugs and to design and develop the efficient therapeutic drugs [4-6].

Since 1920, the intravenous glucose tolerance test (IVGTT) was first introduced as a diagnostic test of the T2DM subject in a way to measure plasma glucose and insulin following glucose injection. The complex dynamic relationship between plasma glucose and insulin are also very interesting to study the glucose-insulin system in the human body. Because of IVGTT data are very informative for studying the glucose-insulin system, then these tests can be also used to study the drug development for assessment of potential new anti-diabetic treatment.

To increase the study duration and frequency of sampling, the IVGTT need be modified. This means the frequently sampled IVGTT data can be used to analyze the modified minimal model which has become a standard tool for analysis of plasma glucose concentration data both for diagnosis or development of a drug effect during this test. The many sampled in the IVGTT was commonly needed, because the individual data will be fitted on the modified minimal model. The fitting curve of the plasma glucose and insulin concentration is used to analyze the parameters describing insulin sensitivity (SI) and glucose efficiency (SG). The glucose concentration profile can show the estimated glucose disappearance in blood, from this estimation can be used as diagnostic of the T2DM subject [7-11].

The aim of this study is to describe how the effect of metformin drug in subjects with T2DM during IVGTT process using the modified minimal model with the pharmacokinetics of metformin. This study to analyze the treatment of T2DM subject using metformin. This mathematical model is the potential to predict the effect of the other anti-hyperglycemic agents in intravenous administration on a T2DM subject.

2. Mathematical model

2.1. Pharmacokinetics model

The relationship between the amount of metformin and its glucose-lowering effect for T2DM subjects after intravenous administration of metformin can be described by the pharmacokinetic model. Transfer of metformin between different compartments was presented with the assumption that occurs according to a coupled first-order kinetic process with corresponding rate constants, can be written as follow [2, 4]:

$$\frac{dX_1}{dt} = X_1(k_{go} + k_{gx}),$$

(1)

$$\frac{dX_2}{dt} = X_2k_{gx} + X_4k_{xg} - X_2k_{gl},$$

(2)

$$\frac{dX_3}{dt} = X_3k_{gl} + X_4k_{pl} - X_3k_{lp},$$

(3)

$$\frac{dX_4}{dt} = X_4k_{lp} - X_4(k_{pg} + k_{pe} + k_{po}) + X_{I},$$

(4)

where variables, $X_1$, $X_2$, $X_3$, and $X_4$, presented the mass of metformin in the gastrointestinal (GI) lumen, GI wall, liver, and periphery compartments, respectively. Variable $X_I$ presented the flow rate of metformin from the intravenous infusion. The rate constants are presented by: $k_{go}$ (min$^{-1}$), drug
elimination via the fecal route; \( k_{gg} \) (min\(^{-1}\)), drug transfer from the GI lumen to the GI wall compartment; \( k_{gp} \) (min\(^{-1}\)), drug transfer from the GI wall to the liver compartment; \( k_{pg} \) and \( k_{gp} \) (min\(^{-1}\)) drug transfer from the liver to the periphery compartment and vice versa; \( k_{gg} \) (min\(^{-1}\)) drug transfer from the periphery to the GI wall compartment; and \( k_{po} \) (min\(^{-1}\)) drug elimination via the urination route. The equations are written in terms of metformin amounts and not concentrations, thereby avoiding the need for estimating the volumes of the pharmacokinetics compartments. In this case, the metformin plasma concentrations are calculated as the mass of metformin divided by the blood flow (20.9 ± 4.1 ml/min/kg body weight).

2.2. Modified minimal model

The first model describing the homeostasis of glucose was developed by Bergman [7]. It is called the 'minimal model'. The minimal model can be used to estimate glucose effectiveness and insulin sensitivity from the intravenous glucose tolerance test (IVGTT) data. After subject fasting, a certain amount of glucose is injected into the bloodstream of the subject, afterward, the blood glucose concentration and insulin concentration are measured for a period of about three hours. This is aimed, to describe those blood glucose concentration and insulin concentration. In this study, the modified minimal model has been proposed. The following variables and parameters are used in the minimal model:

\[
\begin{align*}
    t &= [\text{min}] \text{ time;} \\
    G(t) &= [\text{mg/dl}] \text{ glucose blood concentration at time } t; \\
    I(t) &= [\mu \text{UI/ml}] \text{ insulin blood concentration at time } t; \\
    X(t) &= [\text{min}^{-1}] \text{ function representing the glucose uptake activity by cells, depending on the insulin blood concentration;} \\
    G_b &= [\text{mg/dl}] \text{ normal glucose blood concentration level of a human being;} \\
    I_b &= [\mu \text{UI/ml}] \text{ normal insulin blood concentration level of a human being;} \\
    p_1 &= [\text{min}^{-1}] \text{ rate constant expressing the decrease of glucose caused by glucose uptake by cells, independent of the insulin blood concentration;} \\
    p_2 &= [\text{min}^{-1}] \text{ rate constant expressing the spontaneous decrease of glucose uptake activity by cells;} \\
    p_3 &= [\text{min}^{-2} (\mu \text{UI/ml})^{-1}] \text{ rate constant expressing the increase of glucose uptake activity by cells per unit of insulin blood concentration excess over normal insulin blood concentration level;} \\
    \gamma &= [\text{mg/dl}] \text{ level of glucose blood concentration at which the pancreas releases insulin;} \\
    k &= [\mu \text{UI/ml}] \text{ theoretical insulin blood concentration at time 0 above the normal insulin blood concentration level, after a certain amount of glucose.}
\end{align*}
\]

The modified minimal model is given by [9]:

\[
\begin{align*}
    \frac{dG(t)}{dt} &= p_1(G_b - G(t)) - X(t)G(t), \quad G(t_0) = G_b, \quad (5) \\
    \frac{dX(t)}{dt} &= -p_2X(t) + p_3(I(t) - I_b), \quad X(t_0) = 0, \quad (6) \\
    \frac{dI(t)}{dt} &= \gamma(G(t) - G_b) - k(I(t) - I_b), \quad \text{if } G(t) > G_b, I(t) = I_b, \quad (7) \\
    \frac{dI(t)}{dt} &= -k(I(t) - I_b), \quad \text{if } G(t) < G_b, I(t) = I_b. \quad (8)
\end{align*}
\]

The modified minimal model is formed by two equation parts separately. The first part composed of the equations (5) and (6) that described the glucose blood concentration. The equation form ‘\( p_1(G_b - G(t)) \)’ represents the decrease of glucose caused by the glucose absorption by cells per unit of glucose blood concentration overage normal glucose blood concentration level. However, glucose decreasing is
independent of the insulin concentration. The variable \( \dot{X}(t) \) describes the glucose absorption activity, which depends on insulin. So, the term \( -\dot{X}(t)G(t) \) represents the absorption of glucose by cells, which depends on the insulin blood concentration. The time delay of the effect of insulin on glucose is represented by variable \( X(t) \). The glucose absorption activity decreases linearly, it is presented by the form \( -p_2 \dot{X}(t) \) and will increase when the insulin concentration is above the normal level, as described by the form \( p_3 (I(t) - I_0) \).

The second part is composed of equation (7) and (8) that described the insulin concentration. The form \( \gamma [G(t) - G_0] \) represents an increase of the insulin concentration. The multiplication by \( t \) is assumed that the rate of pancreatic secretion of insulin is directly proportional to the glucose stimulus time. The last form in equation (7) describes a decreasing of insulin per unit of insulin concentration is caused by overage normal insulin concentration level.

The parameters of the modified minimal model are calculated in two steps: the glucose blood concentration is used as input first data on the parameters in the first two equations are derived, the parameters in the last equation are assumed zero input. Input second data used the insulin concentration. The above modified minimal model has been very useful in physiological research. Unfortunately, this model has the following three drawbacks associated with it. First of all, the parameter fitting is divided into two separate parts, as explained above. The input in this model would be better if the parameter fitting is a single-step process. However, this weakness is not a problem again because the glucose-insulin interaction is in a coherent system. Secondly, some results of the mathematical model that produced by this model are not realistic. For example, the modified minimal model does not admit an equilibrium and for certain values of parameters, so the solutions of this model are unbounded. Thirdly, there is not observable variable \( X(t) \), but it is not a problem because of this variable just used to describe the delay of the action of insulin on glucose, due to it just is proposed as artificially. The assumption that the rate of pancreatic secretion of insulin is proportional to the time absorption from the glucose stimulus seems already in accordance with physiology.

Subject with T2DM usually test their blood sugar frequently (1 to 3 times per day), both to assess the effectiveness of their prior metformin dose or to help determine their next metformin dose. For this reason, it is easier to do the blood glucose concentration monitoring through the intravenous measurements. Therefore, the function \( G_b = G_0 - X_d/V_d \) is introduced to describe the metformin concentration in the intravenous. Therefore, an ordinary differential equation that describes this behavior of glucose blood concentration with pharmacokinetics model of metformin is introduced with the following function:

\[
\frac{dG(t)}{dt} = p_1(G_b - G(t)) - \dot{X}(t)G(t), \quad G_b = G_0 - \frac{X_d}{V_d}, \quad (9)
\]

\( V_d \) is the distribution volume in blood that should be estimated in interval 6.67-12.01.

3. Results and Discussion

After subject fasting about 8 to 10 hours, the subject is given injected intravenously of glucose (0.3 g/kg body weight) that be composed 50 percent solution of glucose in distilled water. At the start of the experiment followed by a 5-minute insulin infusion (50 mU/kg body weight) after 20 minutes, this is the standard insulin administration procedure in modified IVGTT test. The venous blood sample was obtained during the three hours. Table I [12] present the experimental data, while the form of the curve derived from these data relating to blood glucose concentration and insulin concentration to time is shown in Figure 1. In Figure 1, profiles of plasma glucose and insulin level are produced by modified minimal model without metformin infusion for type 2 DM subject, with parameters: \( k = 0.121 \text{ [min}^{-1}] \), \( \gamma = 0.0011 \text{ [min}^{-1}] \), \( G_0 = 150 \text{ [mg/dl]} \), \( I_0 = 15 \text{ [μU/ml]} \), \( p_2 = 0.1 \text{ [min}^{-1}] \), \( S_1 = 12.0 \times 10^{-9} \text{ [ml/kg/min.μU/mL]} \), and \( S_0 = 0.022 \text{ [min}^{-1}] \). After an injection of glucose intravenously, the blood glucose concentration rises sharply immediately, then begins to fall with almost equal rises rapidity. However, the fall rate of
glucose is delayed during the two hours. The decreasing rate of the blood glucose concentration varied considerably. In some of the persons, the decreased characteristic of blood glucose decreased to the fasting value just within half an hour, while in others it was still elevated after an hour and a half. In T2DM subjects, the blood sugar was within the non-normal fasting range for two hours.

Table 1. Data of Intravenous Glucose Tolerance Tests on Type 2 DM Subject [12]

| Time (min) | Glucose (mg/dl) | Insulin (µU/ml) | Time (min) | Glucose (mg/dl) | Insulin (µU/ml) |
|------------|-----------------|-----------------|------------|-----------------|-----------------|
| 0          | 170             | 10              | 31         | 254             | 48              |
| 3          | 236             | 12              | 41         | 234             | 35              |
| 8          | 314             | 14              | 50         | 226             | 28              |
| 14         | 306             | 16              | 60         | 202             | 24              |
| 17         | 300             | 90              | 71         | 192             | 22              |
| 22         | 298             | 124             | 80         | 186             | 18              |
| 24         | 294             | 150             | 91         | 192             | 18              |
| 25         | 290             | 184             | 100        | 176             | 18              |
| 27         | 286             | 170             | 111        | 166             | 12              |
| 28         | 278             | 160             | 150        | 164             | 12              |
| 30         | 268             | 114             | 180        | 154             | 12              |

Figure 1. Experiment result of an IVGTT test on the T2DM subject (red circle) and profiles of plasma glucose and insulin level are produced by the modified minimal model without metformin infusion for type 2 DM subject (blue line).

The pharmacokinetics of metformin was best described by a 4-compartmental model with first-order absorption and elimination. This simulation was to explore the pharmacokinetic relationship of metformin on glucose levels after the administration of 500 mg of metformin in type 2 DM. The pharmacokinetics of metformin was assessed using intravenous glucose tolerance tests before and after metformin administration. The dynamic simulation for the combined model is programmed in Matlab and the model parameters are optimized by using clinical data. The relationship between metformin amounts and the glucose-lowering effect is then obtained by solving the set of equations (Eqs. (1)-(9)). Based on the type 2 DM model with and without the metformin treatment, the plasma glucose concentration can be calculated as
shown in Figure 2. In Figure 2, after the intravenous administration of metformin, the plasma glucose concentration decreases rapidly and then decay exponentially. The maximum glucose-lowering effect of the periphery is about 45%. Since the metabolic rate of the corresponding compartment is affected by the treatment of metformin, the plasma glucose concentration is lowered.

Figure 2. Curve profiles of plasma glucose level that is simulated by the modified minimal model with the pharmacokinetics of metformin that was compared with results of an IVGTT test on the T2DM subject before (left) and after (right) intravenously administration of 500 mg of metformin.

4. Conclusions

In this study, the minimal model that be combined a pharmacokinetic model of metformin has been developed for treatment a T2DM subject. The treatment effects of the intravenous metformin are significant. As shown in Figure 2, the plasma glucose concentrations are lowered significantly after the treatment of metformin. This model can be tried to the other anti-hyperglycemic agents for T2DM.

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