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Pharmacokinetic-Pharmacodynamic Study of Metformin Using Oral Glucose Tolerance Test for the Treatment of Type 2 Diabetes Mellitus

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Abstract: In this study, a pharmacokinetic-pharmacodynamic simulation will describe a system of glucose and insulin in the human body based on an oral glucose tolerance test with Metformin treatment. This is presented using the oral glucose tolerance test process by adding glucose absorbed function, insulin secretion in the pancreas, and metformin dose. This model can describe the rate of glucose concentration at the same time as Metformin administration. This model applies to subjects with impaired glucose tolerance (pre-diabetes) and type 2 diabetes mellitus. Experimental data are referenced from research that Møller and co-workers have carried out. This model can describe the reduction rate of glucose. This process reduces hepatic glucose production caused by the glucose absorption rate in peripheral tissues. This model also showed that adding a metformin dose could reduce the glucose concentration. The results of the present model show that the value of the deterministic coefficient (R^2) has reached above 95%, which means that the results of the present model are good.

Keywords: oral glucose tolerance test; pre-diabetes; simulation model; type 2 diabetes mellitus.

Introduction

A mathematical model of pharmacokinetics-pharmacodynamics is usually described only as a profile of the measured concentration and time of a drug administered in blood plasma. The main advantage of the pharmacokinetics-pharmacodynamics model is that this mathematical model is based on the theory of dynamic systems that can describe a drug administration in body response after an administered drug. This mathematical model based on pharmacokinetics-pharmacodynamics can also be used for the intravenous administration of solution drugs (Ďurišová, 2016; Ciccolini et al., 2017; Lazebnik et al., 2022).

In recent years, an oral drug the anti-hyperglycemic, is usually used to control blood glucose in an insulin-dependent diabetes mellitus (IDDM) or type 2 diabetes mellitus (T2DM) is biguanide metformin (dimethyl biguanide). Metformin has been applied for a subject with T2DM, a common disease that combines defects of both insulin secretion and insulin action. Blood glucose concentration levels can be reduced by metformin, predominantly by improving hepatic and peripheral tissue sensitivity to insulin without affecting the secretion of this hormone (Graham et al., 2011; Pala et al., 2007; Scheen, 1996; Sheleme, 2021).

The oral glucose tolerance test (OGTT) is applied clinically to diagnose impaired glucose tolerance (IGT) or prediabetes and T2DM, as a standardized insulin secretion test. The standard OGTT procedure is after an 8-10 hour overnight fast, then 75 g of glucose is administrated orally. It is intended to monitor glucose and insulin concentration levels over time. A prolonged elevation (>120 min) in both blood glucose and insulin

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shows a patient with IGT, it identifies insulin resistance. The standard OGTT can also be used in conjunction with fasting hyperglycemia in diagnosing T2DM (Cobelli et al., 2014; Thewjitcharoen et al., 2019; Bartlette et al., 2021).

To describe the concentration data of glucose and insulin for 2 hours after an oral administration of glucose using an OGTT, it is necessary to develop a mathematical model to assess both the glucose and insulin systems and their interactions. The mathematical model combined with extrapolation and interpolation methods is used to measure insulin secretion and sensitivity. It is commonly called the oral glucose minimal model (Seike et al., 2011; Kartono et al, 2017).

Sun and co-authors have introduced a pharmacokinetics-pharmacodynamics (PK-PD) model of metformin for the treatment of T2DM. This model describes the relationship between the measured concentration and time of the metformin drug. This model also describes the glucose-lowering effect for subjects with T2DM after intravenous and oral administration of metformin. It is constituted of three compartments including the gut, liver, and periphery (Sun et al., 2011).

This study proposes a new model based on the OGTT and pharmacokinetic-pharmacodynamic models to analyze the action of metformin drugs in subjects with IGT and T2DM during an OGTT. This model is expected to explain the mechanism relevant to drug administration and the body's response to oral drug administration.

Mathematical Model

The Modified Oral Glucose Minimal Model

A mathematical model of the glucose and insulin as a dynamic system method of test results from 2-h OGTTs as one of the diagnostic criteria for pre-diabetes and T2DM is the standard test by the World Health Organization (WHO). Seike and co-workers have introduced a mathematical model of the oral glucose minimal model to provide an accurate method for assessing insulin secretion and insulin sensitivity in pre-diabetes and T2DM during an OGTT protocol (Seike et.al., 2011; Kartono et.al, 2017). In this study, we will modify the oral glucose minimal model with a function of the orally administered glucose being absorbed from the intestines before entering the systemic circulation (Seike et.al., 2011; Kartono et.al, 2017). The minimal model was modified with the addition of an oral glucose function. This model takes the form of two coupled ordinary differential equations. The first equation describes the rate of plasma glucose concentration, while the second describes the rate of insulin concentration:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b + \frac{R_\alpha}{V}, \quad G(t_0) = G_0 \tag{1}$$

$$\frac{dX(t)}{dt} = -p_2(t) + p_3[I(t) - I_b], \quad X(t_0) = 0 \tag{2}$$

$$R_\alpha(t) = \begin{cases} \alpha_{i-1} + \frac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}}(t - t_{i-1}) \\ 0 \end{cases}$$

$$\begin{cases} t_{i-1} \le t \le t, i = 1 \ldots 8 \\ \text{others} \end{cases} \tag{3}$$

The R_I parameter describes the rate of pancreatic insulin secretion. The parameter R_I consists of two components: (1) dynamic insulin secretion (R_{I1}) and (2) static insulin secretion (R_{I2}). The rate parameter p_{I1} (min^{-1}) describes the circulating rate for insulin loss. The total insulin rate (dI/dt) of the single-compartment model is determined by the following equation:

$$\frac{dI(t)}{dt} = -p_{I1}[I(t) - I_b] + R_{I,} \quad I(t_0) = I_b \tag{4}$$

$$R_I = R_{I1} + R_{I2} \tag{5}$$

The parameter R_{I1} (μU.mL^{-1}.min^{-1}) describes the rate of insulin secretion stored in β-cells. This is in response to increased levels of glucose concentration:

$$R_{I1} = \begin{cases} p_{I2}\frac{dG}{dt}, & \frac{dG}{dt} > 0 \\ 0, & \frac{dG}{dt} \le 0 \end{cases} \tag{6}$$

where the parameter p_{I2} (μU.mL^{-1}.mg^{-1}.dL) represents the rate of dynamic insulin secretion by β-cells. New insulin secretion induced in response to increased glucose concentration levels is described by the parameter R_{I2}:

$$\frac{dR_{I2}}{dt} = \begin{cases} -\frac{1}{p_{I3}}[R_{I2} - p_{I4}(G - G_b)], & G - G_b > 0 \\ -\frac{1}{p_{I3}}R_{I2}, & G - G_b \le 0 \end{cases} \tag{7}$$

where the parameter p_{I4} (μU.mL^{-1}.mg^{-1}.dL.min^{-1}) describes the rate of static insulin secretion by β-cells caused by an increase in glucose levels with the time constant parameter p_{I3} (min).

Pharmacokinetics Model

In this study, the pharmacokinetic-pharmacodynamic model is used to describe the mass of oral metformin in a periphery compartment. A mass of

oral metformin is combined with the OGTT model during an OGTT to predict its glucose-lowering effect for the subject with pre-diabetes and T2DM after oral administration of metformin. A set coupled first-order kinetic function with corresponding rate constants process along the mass transfer of oral metformin between different compartments was presented by (Sun et al., 2011):

$$\frac{dX_1}{dt} = X_1(k_{go} + k_{gg}) + X_o \quad (8)$$

$$\frac{dX_2}{dt} = X_1 k_{gg} + X_4 k_{sg} - X_2 k_{gl} \quad (9)$$

$$\frac{dX_3}{dt} = X_2 k_{gl} + X_4 k_{pl} - X_3 k_{lp} \quad (10)$$

$$\frac{dX_4}{dt} = X_3 k_{lp} - X_4(k_{pl} + k_{pg} + k_{po}) \quad (11)$$

where the variables, X_1, X_2, X_3, and X_4, represent the mass of metformin in the gastrointestinal (GI) lumen, GI wall, liver, and peripheral compartment. The variable X_O represents the flow rate of metformin from oral administration with the rate constant represented by k_{go} (min^{-1}). The rate of drug elimination via feces is expressed by k_{gg} (min^{-1}). The rate of drug transfer from the GI lumen to the GI wall compartment is expressed by k_{gl} (min^{-1}). The rate of drug transfer from the GI wall to the liver compartment is presented by k_{lp} and k_{pl} (min^{-1}). The rate of drug transfer from the liver to the peripheral compartment and vice versa is expressed by k_{pg} (min^{-1}). The rate of drug elimination via the urinary tract is given by k_{po} (min^{-1}). The equations are written in mass quantities of metformin and not concentrations, in order to avoid estimating the volume of the pharmacokinetic-pharmacodynamic compartment. The plasma concentration of metformin was calculated as the mass of metformin divided by blood flow (20.9 ± 4.1 ml/min/kg body weight).

The Modified Oral Glucose Minimal Model with Pharmacokinetics Model of Metformin

The function $G_b = G_0 - \frac{X_4}{V_d}$ is introduced which describes the glucose concentration in the periphery compartments. A differential equation describing this behavior of glucose blood concentration with the pharmacokinetics model of metformin is introduced with the following function:

$$\frac{dG(t)}{dt} = p_1(G_b - G(t)) - X(t)G(t)\,,$$
$$G_b = G_0 - \frac{X_4}{V_d}\,, \quad (12)$$

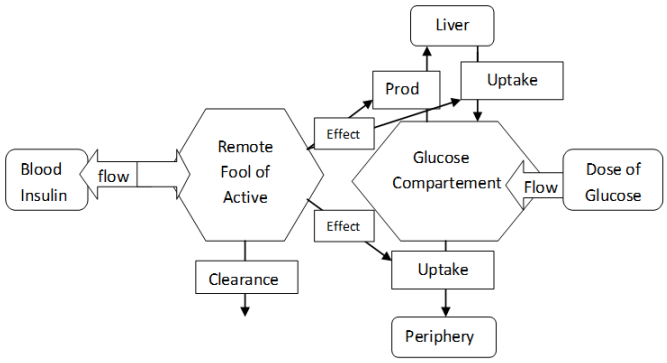


Figure 1 The mechanism scheme of the modified oral glucose minimal model

Table 1. Variables and parameters of Oral Glucose Minimal Model.

Symbol	Unit	Notes
$G(t)$	mg/dL	glucose concentration at a certain t, after administration of glucose input orally
$I(t)$	µU/mL	insulin concentration at a certain t, after glucose is administered orally
$X(t)$	min^{-1}	insulin concentration at a certain t, after glucose is administered orally
G_b	mg/dL	basal glucose concentration, before glucose is given orally
I_b	µU/mL	basal insulin concentration, before glucose is administered orally
G_0	mg/dL	glucose concentration when t is zero
I_0	µU/mL	insulin concentration when t is zero
p_1	min^{-1}	rate of glucose uptake without insulin in tissues
p_2	min^{-1}	rate of increase in the ability of glucose uptake
p_3	min^{-2}(µU/mL)$^{-1}$	rate of glucose-dependent uptake of insulin in tissues
$R_a(t)$	mg. kg^{-1}min^{-1}	rate of endogenous glucose input into the systemic circulation
V	dL/kg	volume of glucose distribution
a_i	mg. kg^{-1}min^{-1}	glucose uptake rate
t_i	min	glucose absorption time

Result and Discussion

The simulation of the combined model between the modified minimal oral glucose and the pharmacokinetic-pharmacodynamic model will be

programmed using MATLAB. It is to facilitate numerical calculations and graphing of glucose and insulin concentrations. The parameters of the model are optimized using experimental data. The analysis of these parameters uses a deterministic coefficient (R^2). This is necessary to know the validation value between experimental data and model results. The deterministic coefficient (R^2) is formulated by:

$$X^2 = \sum_{i=1}^{N} \left[\frac{y_i - y(t_i)}{\sigma}\right] \quad (13)$$

$$SST = \sum_{i=1}^{N} \left[\frac{y_i - \overline{y}}{\sigma}\right]^2 \quad (14)$$

$$R^2 = 1 - \frac{X^2}{SST} \quad (15)$$

where y_i is experimental data that contains deviation standard σ, $y(t_i)$ is model results, N is all data and $\overline{y}$ is the average value of the sum from experimental data and model results.

Optimization of the parameters of the modified minimal oral glucose model has been carried out. The range of values for model input is given in Table 2. Then the model results were extrapolated and interpolated using experimental data from observed glucose and insulin concentrations (Møller et.al., 2014). The model calculation results are shown in Figures 2(a) and 3(a). At 300 minutes, the glucose concentration returned to the basal level. However, based on the curve results reported in Figures 2(a) and 3(a), the peak points between IGT and T2DM are different. The difference in the peak points in the curve can identify the parameter values related to insulin secretion. These parameters are also related to glucose metabolism. The estimated parameters can be used as a diagnostic analysis of subjects with IGT or T2DM.

This study uses a pharmacokinetic-pharmacodynamic model as a system theory of glucose dynamics that can predict the dynamic relationship between oral drug intake in the human body. The prediction profile is expressed between glucose concentration and time, as shown in Figures 2(b) and 3(b). The present model can be used clinically so that the estimated drug dose administered can be predicted by the present model.

In the present model, the simulation of the modified oral glucose minimal model combined with and without (the pharmacokinetic-pharmacodynamic model) for subjects with IGT have calculated as shown in Figure 2. In Figure 2(a), the value of the deterministic coefficient (R^2) between the experimental data and the present model yield is above 95%. In Figure 2(b), after oral administration of metformin (500 mg), the plasma glucose concentration decreased slowly and then decayed exponentially. Due to metformin treatment, plasma glucose concentrations are low. The peak plasma glucose concentration without the effect of metformin is approximately 190 mg/dL which is reached after 50 minutes. In this present model, the peak plasma glucose concentration is approximately 150 mg/dL after administration of the drug.

The simulation was also carried out on subjects with T2DM, as shown in Figure 3. In Figure 3(a), the value of the deterministic coefficient (R^2) between the experimental data and the current model results is above 95%. Glucose concentration in subjects with T2DM decreased significantly after the administration of metformin (500 mg). The concentration peak of plasma glucose with the effect of metformin is around 250 mg/dL which is reached after 75 minutes. Then the glucose concentration will decrease to basal glucose. The current model has shown that oral administration of metformin produces significant plasma glucose-lowering effects.

The results of the present model have shown that it has the potential to be an accurate tool for controlling subjects with pre-diabetes or diabetes in clinical practice with metformin administration. Analysis based on OGTT for 5 hours showed a good correlation between experimental data and model results. Therefore, OGTT for 5 hours has been used for the diagnosis of diabetes based on WHO criteria. This method is also more cost-effective and not time-consuming to apply clinically. Current model accuracy estimates with experimental data obtained from OGTT for 5 hours (Møller et.al., 2014).

Table 2. Parameters value of this present model.

Parameters	Values
G_b	115-160
I_b	10-20
G_0	115-160
I_0	10-20
p_1	0.05-0.2
p_2	0.0001-0.0003
p_3	$1.0 - 4.0 \times 10^{-4}$
k_{go}	$1.50 - 2.0 \times 10^{-3}$
k_{gg}	$1.80 - 2.2 \times 10^{-3}$
k_{gl}	0.40 - 1.00
k_{lp}	0.70 - 0.10
k_{pl}	$1.0\text{-}1.2 \times 10^{-2}$
k_{pg}	3.0 - 5.0
k_{po}	0.20 - 0.60

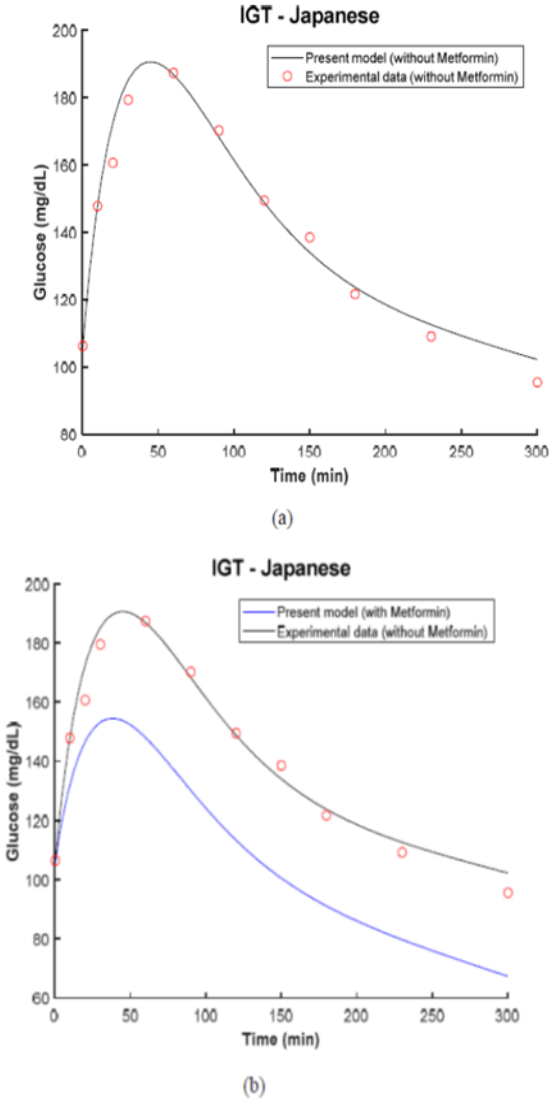
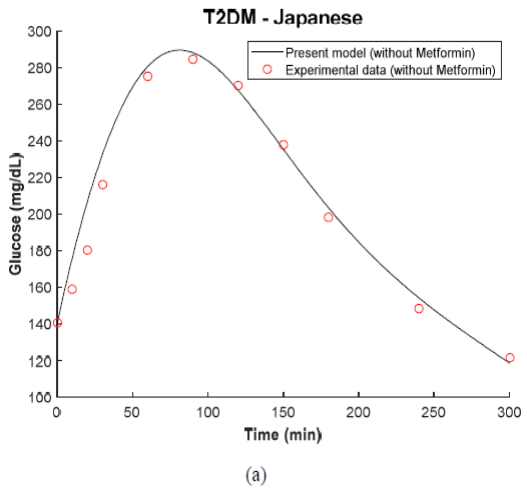


Figure 2 (a) Plasma glucose concentration of IGT patients before following the administration of metformin (500 mg) and (b) after following the administration of metformin (500 mg).



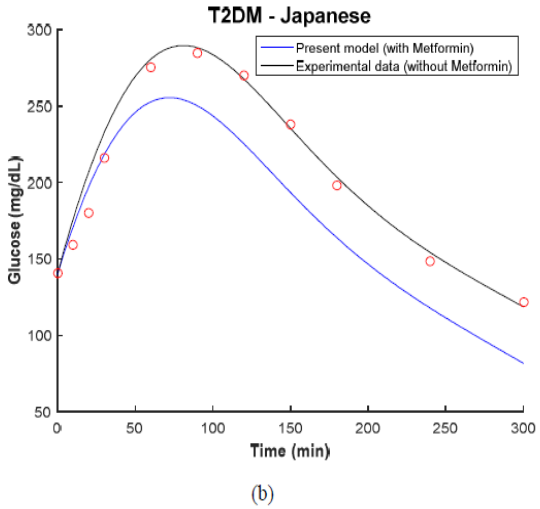


Figure 3 (a) Plasma glucose concentration of T2DM patients before following the administration of metformin (500 mg) and (b) after following the administration of metformin (500 mg).

Conclusion

This model can present the successful use of a mathematical model from the theory of the pharmacokinetic-pharmacodynamic dynamic systems of an oral drug of metformin. The simulation results clearly show that the effects of the treatment using metformin can significantly lower the glucose concentration than no therapy of metformin. This present model has also shown successfully described the pharmacokinetic-pharmacodynamic simulation of metformin administrated orally to IGT and T2DM subjects. For future works, this present model will be used with some other oral drugs of anti-hyperglycemic for the IGT and T2DM subjects, to evaluate the accuracy of this present model.

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References

Bartlette, K., Carreau, A.M., Xie, D., Garcia-Reyes, Y., Rahat, H., Pyle, L., Nadeau, K.J., Cree-Green, M., & Diniz Behn, C., (2021). Oral minimal model-based estimates of insulin sensitivity in obese youth depend on oral glucose tolerance test protocol duration. Metabolism Open 9, 100078.

Ciccolini, J., Barbolosi, D., Meille, C., Lombard, A., Serdjebi, C., Giacometti, S., Padovani, L., Pasquier, E., & André, N. (2017). Pharmacokinetics and Pharmacodynamics-Based Mathematical Modeling Identifies an Optimal Protocol for Metronomic

Chemotherapy. Cancer Research. 77(17), 4723-4733.

Cobelli, C., Man, C.D., Toffolo, G., Basu, R., Vella, A., & Rizza, R. (2014). The Oral Minimal Model Method, Diabetes 63(4), 1203–1213.

Ďurišová, M. (2016). Mathematical Models of the Pharmacokinetic Behavior of Acetaminophen in Rats, Journal of Analytical & Pharmaceutical Research 3(2), 54-60.

Lazebnik, T., Weitman, H., Kaminka, G.A. (2022) Generic Purpose Pharmacokinetics-Pharmacodynamics Mathematical Model For Nanomedicine Targeted Drug Delivery: Mouse Model. bioRxiv.

Graham, G.G., Punt, J., Arora, M., Day, R.O., Doogue, M.P., Duong, J.K., Furlong, T.J., Greenfield, J.R., Greenup, L.C., Kirkpatrick, C.M., Ray, J.E., Timmins, P., & Williams, K.M. (2011) Clinical pharmacokinetics of metformin. Clinical Pharmacokinetics. 50(2), 81-98.

Kartono, A., Putri, E.S., Setiawan, A.A., Syafutra, H., & Sumaryada, T. (2017). Study of Modified Oral Minimal Model using *n*-Order Decay Rate of Plasma Insulin for the Oral Glucose Tolerance Test in Subjects with Normal, Impaired and Diabetic Glucose Tolerance, American Journal of Applied Sciences 14(4), 426-435.

Møller, J.B., Man, C.D., Overgaard, R.V., Ingwersen, S.H., Tornøe, C.W., Pedersen, M., Tanaka, H., Ohsugi, M., Ueki, K., Lynge, J., Vasconcelos, N.M., Pedersen, B.K., Kadowaki, T., & Cobelli, C., (2014). Ethnic differences in insulin sensitivity, β-cell function and hepatic extraction between Japanese and Caucasians: A minimal model analysis, The Journal of Clinical Endocrinology & Metabolism 99(11), 4273–4280.

Pala, L., Mannucci, E., Dicembrini, I., & Rotella, C.M., (2007). A Comparison of Mealtime Insulin Aspart and Human Insulin in Combination with Metformin in Type 2 Diabetes Patients, Diabetes Research and Clinical Practice 78(1), 132-135.

Scheen, A.J. (1996). Clinical Pharmacokinetics of Metformin. Clinical Pharmacokinetics. 30, 359–371.

Seike, M., Saitou, T., Kouchi, Y., Ohara, T., Matsuhisa, M., Sakaguchi, K., Tomita, K. Kosugi, K., Kashiwagi, A., Kasuga, M. Tomita, M., Naito, Y., & Nakajima, H. (2011). Computational assessment of insulin secretion and insulin sensitivity from 2-h oral glucose tolerance tests for clinical use for type 2 diabetes, The Journal of Physiological Sciences. 61, 321–330.

Sheleme, T. (2021) Clinical Pharmacokinetics of Metformin. Metformin - Pharmacology and Drug Interactions, IntechOpen.

Sun, L., Kwok, E., Gopaluni, B., & Vahidi, O. (2011) Pharmacokinetic-Pharmacodynamic Modeling of Metformin for the Treatment of Type II Diabetes Mellitus, Open Biomedical Engineering Journal. 5, 1-7.

Thewjitcharoen, Y., Jones Elizabeth, A., Butadej, S., Nakasatien, S., Chotwanvirat, P., Wanothayaroj, E., Krittiyawong, S., Himathongkam, T., & Himathongkam, T. (2019) Performance of HbA1c versus oral glucose tolerance test (OGTT) as a screening tool to diagnose dysglycemic status in high-risk Thai patients. BMC Endocrine Disorders 19, 23.