PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF METFORMIN FOR THE TREATMENT OF TYPE Ⅱ DIABETES MELLITUS

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ABSTRACT

Metformin is an antihyperglycemic agent commonly used for the treatment of Type II diabetes mellitus. However, its effects on patients are derived mostly from clinical experiments. In this current study, a dynamic model of metformin combined with a Type II diabetic physiological model is proposed. The metformin model is based on the pharmacokinetic and pharmacodynamic relationship with a human body. The Type II diabetic model is a modification of an existing compartmental diabetic model. The corresponding model parameters are estimated by optimization using the clinical data from published reports. From the dynamic simulation, the combination treatment of insulin infusion plus oral metformin is shown to be superior than the monotherapy with metformin only. This result is consistent with clinical understanding of the use of metformin and insulin treatments. The model can be further analyzed for evaluating the treatment of diabetes mellitus with different pharmacological agents.

INTRODUCTION

Metformin has been used as a glucose-lowering agent in Type II diabetes mellitus since 1957. Nearly 40 years later, it was approved in the United States and rapidly gained wide acceptance [1-3]. In recent years, pharmacokinetic-pharmacodynamic (PK-PD) modeling has become a key factor of success in modern drug discovery and development [4]. The use of PK-PD modeling in translational drug research is a promising approach that provides better understanding of the underlying kinetic phenomena involved with the study of absorption, distribution, metabolism and excretion of drugs.

There are continuing efforts to develop the PK and PD models in order to optimize therapy. D'Argenio and Schumitzky (1979) published a kind of software to estimate the parameters for the PK models [5], Stepensky *et al*. (2001) presented the plasma glucose-lowering effect for oral metformin treatment in diabetic rats [6], and Pentikäinen *et al*. (1979) described the pharmacokinetics of the plasma metformin concentration in healthy volunteers [7]. Lee and Kwon (2004) also developed a PK-PD model to describe the relationship between plasma concentration of metformin and its glucose-lowering effect based on the study of healthy volunteers [8].

In preliminary investigations from the literature, the glucose-lowering effect of metformin is apparently composed of a combination of several distinct activities in various organs and tissues [9,10], including the liver, gastrointestinal tract, blood and tissues [11]. However, all of these studies focused on the efficacy and safety of metformin based on experimental studies. On the other hand, mathematical modeling of glucose-insulin interaction in a normal body has been studied since 1961 [12]. A few physiologic models using anatomical organs and tissue compartments have been proposed for simulating glucose metabolism and its regulation by insulin and glucagons in a healthy body [13,14]. Their main application was to simulate the physiological dynamics for Type I diabetic patients. Vahidi *et al.* (2010) recently proposed a substantial modification of the compartmental model for Type II diabetic patients who are characterized by multiple abnormalities in the pancreas, body tissues and liver [15]. Because of many limitations in carrying out human experimental studies, a dynamic modeling approach of combining the PK-PD model of metformin with the Type II diabetic patient model is the objective of this research work. Since the combined treatment of insulin infusion and oral hypoglycemic agents (OHA) is often used in moderate-to-severe Type II diabetic patients with secondary failure of OHA [16], the proposed model can be analyzed to compare the monotherapy with metformin only and the combination treatment of insulin infusion plus oral metformin in Type II diabetic patients.

This paper will first describe the development of the dynamic model, followed by a comparison of the simulated results and human clinical data obtained from the literature.

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MODELING

The modeling of metformin in a human body follows the idea of compartmental modeling of diabetic patients. The human body is represented by six physiologic compartments as shown in Fig. 1. The solid lines show the blood flow directions, the point-dash lines indicate the distribution of metformin, and the rectangular blocks represent different compartments. Muscles and body tissues are represented as a single periphery block. The gastrointestinal (GI) lumen and GI wall are lumped into the gut compartment. The model of Type II diabetic patients also includes six similar compartments. For the glucose-lowering effect of metformin, it is composed of a combination of distinct activities in three organs and tissues [17], including the gut, liver and periphery. Therefore a multi-compartmental PK model is used to describe the pharmacokinetics of metformin.

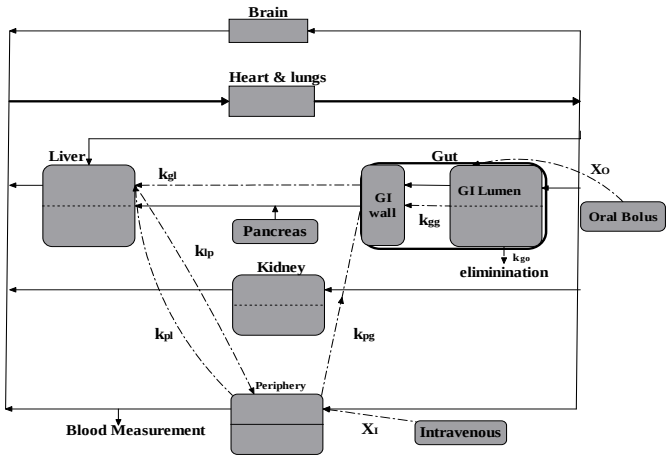

Figure 1: Schematic diagram of the compartmental model for metformin

PK Model

Based on the clinical literature, the effects of metformin mainly include: decreased hepatic glucose output [18]; reduced rate of intestinal glucose absorption [19]; and increased glucose uptake by muscle cells and adipocytes [20]. The accumulation of metformin in the GI wall is not only through the GI lumen, but also via arterial blood supply to the intestine (with the rate constant k_{pg}). Therefore, in the gut compartment, both the GI lumen and GI wall need to be accounted for in the PK modeling. The followings are the modeling equations for the different compartments:

$$dX_1/dt = -X_1(k_{go} + k_{gg}) + X_O \quad (1)$$

$$dX_2/dt = X_1 k_{gg} + X_4 k_{pg} - X_2 k_{gl} \quad (2)$$

$$dX_3/dt = X_2 k_{gl} + X_4 k_{pl} - X_3 k_{lp} \quad (3)$$

$$dX_4/dt = X_3 k_{lp} - X_4(k_{pl} + k_{pg} + k_{po}) + X_I \quad (4)$$

where X_1, X_2, X_3, and X_4 are the concentrations of metformin in the GI lumen, GI wall, liver, and periphery compartments, respectively. X_O is the concentration of metformin as a result of a single oral ingestion, and the X_I is the concentration of metformin from intravenous infusion. The rate constants are: k_{go}, drug elimination via the fecal route; k_{gg}, drug transfer from the GI lumen to the GI wall compartment; k_{gl}, drug transfer from the GI wall to the liver compartment; k_{lp} and k_{pl}, drug transfer from the liver to the periphery compartment and similar transfer in the opposite direction, k_{pg}, drug transfer from the periphery to the GI wall compartment; and k_{po}, drug elimination via the urination route. In this modeling approach, metformin is distributed to the GI lumen, liver, and periphery compartment following oral and intravenous modes of administration.

The compartmental model with first-order absorption is used to describe the kinetics of the intravenous administration. The model structure is described by following equation,

$$X_I = A'e^{-\alpha t} + B'e^{-\beta t} + C'e^{-\gamma t} \quad (5)$$

where X_I is the plasma concentration at the end of the infusion; and α , β and γ are the rate constants during the exponential phases. The parameters are estimated by optimization using experimental data points.

For the oral administration, the pharmacokinetics of metformin from mouth to the GI lumen was described according to eq. (6),

$$X_O = Ae^{-\alpha' t} - Be^{-\beta' t} \quad (6)$$

where α' and β' are rate constants; A and B represent the contribution of the corresponding exponentials. These parameters are also estimated by optimization using experimental data points.

PK-PD model

The transient changes of metformin concentration at different biophases can be obtained through the PK model described in the earlier section. To generate the glucose-lowering effect of metformin, a PK-PD model is proposed in the following. Since the overall glucose-lowering effect of metformin is attributed to the inhibition of glucose production or stimulation of glucose utilization at the individual biophases, it can be calculated by using the metabolic rate of glucose

relative to the baseline metabolic rate of glucose as follows:

$$E_x = \frac{\left| r_x^b - r_x^{PK-PD} \right|}{r_x^b} \quad (7)$$

where E_x represents the overall glucose-lowering effect in the x compartment which includes the GI tract, liver and periphery; the r^b indicates the baseline metabolic rate; and r_x^{PK-PD} is the metabolic rate of glucose at the x compartment following metformin administration. However, E_x cannot be calculated directly from eq. (7) as the metabolic rates are unknown. According to reference the literature published by Stepensky *et al*. (2001) [17], the glucose-lowering effects for the three compartments can be calculated as follows:

$$E_{GI} = \frac{\nu_{GI,max} \times (X_2)^{n_{GI}}}{(\varphi_{GI,50})^{n_{GI}} + (X_2)^{n_{GI}}} \quad (8)$$

$$E_L = \frac{\nu_{L,max} \times (X_3)^{n_L}}{(\varphi_{L,50})^{n_L} + (X_3)^{n_L}} \quad (9)$$

$$E_P = \frac{\nu_{P,max} \times (X_4)^{n_P}}{(\varphi_{P,50})^{n_P} + (X_4)^{n_P}} \quad (10)$$

where E_{GI} and E_P are the stimulation of glucose utilization in the GI tract (GI) as well as by muscle and fat tissues (P), respectively; E_L indicates the inhibition of glucose production in the liver (L); ν is the parameter presenting the maximum effect of the metformin in each compartment ($\nu_{GI,max}$, $\nu_{L,max}$, and $\nu_{P,max}$); φ is the metformin concentration at the biophase that produce 50% of the maximal effect ($\varphi_{GI,50}$, $\varphi_{L,50}$, and $\varphi_{P,50}$); and n_L, n_{GI}, and n_P are the shape factor. The model parameter estimation is an iterative process, and the parameters are fitted with the published data set from the literature published by Stepensky *et al*. (2001) [17].

PK-PD model in combination with the Type II diabetic model

The PK-PD model related the metformin concentration in different compartments to the glucose-lowering effect. However, simply based on this model alone, the plasma glucose and insulin concentration for Type II diabetic patients are still unavailable. Thus it is necessary to combine the PK-PD model with the physiological model for Type II diabetic patients to simulate the effect of metformin on patients with Type II diabetes mellitus.

With the metformin treatment, the metabolic rate of different substances should be adjusted according to their specific effects. For the simulation of Type II diabetic patients, the rate of gut glucose utilization with no metformin effect (r_{GGU}) is calculated internally by the dynamic model developed by Vahidi *et al.* (2010). Because metformin is known to increase the glucose utilization by the gut, the rate of gut glucose utilization (r_{GGU}^{PK-PD}) in the Type II diabetic model is modified as shown in eq. (11).

$$r_{GGU}^{PK-PD} = (1 + E_{GI}) r_{GGU} \quad (11)$$

Similarly, metformin is known to lower hepatic glucose production, the rate of hepatic glucose production (r_{HGP}^{PK-PD}) is modified as shown in eq. (12),

$$r_{HGP}^{PK-PD} = (1 - E_L) r_{HGP} \quad (12)$$

where r_{HGP} is the rate of the hepatic glucose production without the consideration of metformin for the Type II diabetic patients. Also, the rate of the periphery glucose uptake (r_{PGU}^{PK-PD}) is modified to the following equation:

$$r_{PGU}^{PK-PD} = (1 + E_P) r_{PGU} \quad (13)$$

where r_{PGU} is the rate of the periphery glucose uptake without the treatment of metformin. The rest of the Type II model is based on the one developed by Vahidi *et al*. (2010), and the Type II model parameters remain the same as originally proposed by Vahidi *et al*. (2010).

RESULTS AND DISCUSSION

The dynamic simulation for the combined model is programmed in Matlab. The model parameters are optimized by using experimental human data obtained from the literature.

For the mode of intravenous administration, a set of experimental data from healthy volunteers published by Pentikäinen *et al*. (1979) [7] is used to optimize the model parameters. For the mode of oral administration, a set of data obtained from twenty-two healthy male volunteers via the oral metformin treatment published by Lee and Kwon (2004) [8] is used to adjust the parameters of the PK model. Through the optimization, the parameters of the PK-PD model are shown in Table 1.

Table 1: Parameters of the PK-PD model

PK-PD Parameters			
A' (mcg/ml)	15	β'	0.1
B' (mcg/ml)	7.5	k_{go} (min^{-1})	1.88e-03
C' (mcg/ml)	1.5	k_{gg} (min^{-1})	1.85e-03
A (mcg/ml)	19	k_{gl} (min^{-1})	0.458
B (mcg/ml)	19	k_{lp} (min^{-1})	0.910
α	12.8	k_{pl} (min^{-1})	1.01e-02
β	1.9	k_{pg} (min^{-1})	4.13
γ	0.403	k_{po} (min^{-1})	0.509
α'	0.06		

A set of published data tested from the Type II diabetic patients aged 30-65 years old following the basal insulin in combination with metformin treatment was used to verify the proposed model and compare the different modes of metformin treatment. In this set of data, all patients firstly received human insulin (0.1 U/kg) before breakfast, lunch and dinner, plus metformin (500 mg) after meals. Blood glucose and lipids were measured before and at 30 min intervals for 3 h after a standard meal [16].

Based on the developed PK-PD model for Type II diabetic patients, the same mounts of insulin and metformin are given. The simulated results are compared with the published data and the case of single metformin treatments (see Fig. 2).

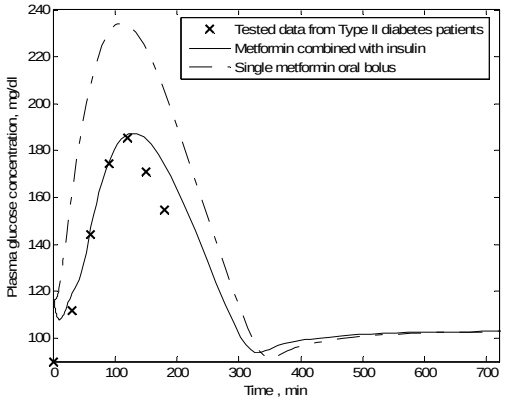

Figure 2: Plasma glucose concentration of Type II diabetic patients following the administration of metformin (500mg) in combination with human insulin (0.1 U/kg) and single metformin (500mg).

In Fig. 2, the simulated results clearly show that the model is able to describe well the dynamics of using metformin as a monotherapy. The effects of the combination treatment using both metformin and insulin infusion are significantly better than the monotherapy of metformin alone.

CONCLUSION

In present work, a PK-PD model has been developed for Type II diabetic patients. The glucose lowering affects have been demonstrated by comparing the predicted outcomes with clinical data. The treatment effects of metformin monotherapy and combination therapy with both metformin and insulin have also been demonstrated.

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