Mechanism Based Pharmacokinetic Pharmacodynamic Modeling of Vildagliptin as an Add-on to Metformin for Subjects with Type 2 Diabetes

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Abstract: Various drugs are used to maintain normoglycemia in subjects with type 2 diabetes mellitus. The combination of the drugs from different classes in one single tablet may enhance the effectiveness of the anti-diabetic drugs. To investigate the impact of combining drugs on the glucose regulation of subjects with type 2 diabetes, we propose a pharmacokinetic/pharmacodynamics (PK/PD) mathematical modeling approach for a combination of metformin and vildagliptin drugs. In the proposed modeling approach, two separate PK models representing oral administration of metformin and vildagliptin for diabetic subjects are interconnected to a PD model comprising a detailed compartmental physiological model representing the regulatory effect of insulin, incretins and glucagon hormones on glucose concentration in a human body. The impact of doses of individual drugs and their combination on the blood glucose concentration of a group of type 2 diabetic subjects is investigated. It is indicated that while administration of individual drugs reduces the blood glucose levels, since they have separate mechanisms of action, combining them synergizes lowering the blood glucose levels.

1 Introduction

Several anti-diabetic drugs have been developed over the past hundred years. Perhaps, exogenous insulin has been the first drug used practically to control the blood sugar in patients with diabetes since 1920s [White (2014)]. For type 1 diabetes, exogenous insulin is the only medication used to control the blood sugar due to the lack of endogenous insulin production caused by fully destruction of the subjects' pancreatic beta cells. However, in case of type 2 diabetes, since high blood sugar is attributed to the multiple abnormalities in different body organs of the diabetic subjects [Vahidi, Gopaluni and Ezra (2015)], several classes of anti-diabetic drugs each of which are effective on specific organs have been introduced to the market [White (2014)].

Metformin, a member of biguanide class of anti-diabetic drugs, has been used as an oral anti-hyperglycemic agent in France since 1957 [Stargrove, Treasure and McKee (2008)] and has been administered as the initial preferred anti-diabetic drug for subjects with type

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2 diabetes for many years [Rhee, Chung, Yi et al. (2017)]. It received approval from the United States Food and Drug Administration (FDA) on 1994 and used in the US market since then [Howlett and Bailey (1999)]. Metformin lowers the blood sugar by suppressing hepatic glucose production [Kirpichnikov, McFarlane and Sowers (2002)], enhancing peripheral glucose uptake resulted from increased insulin sensitivity [Bailey and Turner (1996)] and increasing intestinal glucose consumption [McCreight, Bailey and Pearson (2016)]. Vildagliptin, a member of dipeptidyl peptidase 4 (DPP-4) inhibitors, is a new oral anti-hyperglycemic drug used in more than 76 countries [Landersdorfer, He and Jusko (2012a)]. DPP-4 inhibitors decrease the blood glucose concentration by prolonging the circulation of active glucagon like peptide 1 (GLP-1), one of the two most important incretin hormones, by inhibiting DPP-4 enzyme responsible for deactivating the GLP-1 [Landersdorfer, He and Jusko (2012b)].

Combination of drugs from different classes to complement each other's action may enhance the drugs medical impact on the diabetic subjects. Since biguanids and DPP-4 inhibitors have different mechanisms and sites of action, polytherapy of vildagliptin as an add-on to the metformin has been the topic of some recent studies [Berndt-Zipfel, Michelson, Dworak et al. (2013); Blüher, Kurz, Dannenmaier et al. (2012); Halimi, Schweizer, Minic et al. (2008); Ji, Pan, Lu et al. (2013); Tang, Wang, Jiang et al. (2015)]. Clinical trials on human subjects have indicated that their combination enhances the blood sugar control in subjects with type 2 diabetes. While human experimentations have been conducted to prove the hypothesis, they are very expensive and sometimes impossible to be performed due to the medical restrictions. They should also meet ethical concerns and may results in unpredicted side effects for subjects. Pharmacokinetic/pharmacodynamic (PK/PD) mathematical modeling of drugs is another alternative which enables investigating the effects of drugs on the subjects in computer environment.

A few studies have been published on PK/PD mathematical modeling of vildagliptin [Landersdorfer, He and Jusko (2012a, 2012b)] and metformin [Lee and Kwon (2004); Stepensky, Friedman, Raz et al. (2002); Sun, Kwok, Gopaluni et al. (2011)] so far. Lee et al. [Lee and Kwon (2004)] proposed a one equation indirect response model to represent the metformin glucose lowering effect in human diabetic subjects. Using a similar approach, Stepensky et al. [Stepensky, Friedman, Raz et al. (2002)] simulated the glucose lowering effect of metformin by an indirect response model on diabetic rats. The main difference between the two research studies was considering the number of compartments to represent the glucose concentration in the body. In Lee and Kwon study, the whole human body was considered as one physiological compartment while Stepensky et al. simulated the metformin glucose lowering effect within three compartments including liver, gastrointestinal (GI) tract and systemic circulation (comprising blood, different organs and tissues). The Stepensky et al. model was later used by Lin et al. for type 2 diabetic human subjects [Sun, Kwok, Gopaluni et al. (2011)]. Using clinical data from human subjects, they indicated that the Stepensky et al. model structure can be used to predict the pharmacokinetics and pharmacodynamics of metformin on human subjects by updating the model parameters. In terms of vildagliptin, Landersdorfer et al. [Landersdorfer, He and Jusko (2012a); Landersdorfer, He and Jusko (2012b)] considered a two compartment model, central and peripheral compartments, to represent the vildagliptin pharmacokinetics. To model its pharmacodynamics, they considered a four

compartment model, three for glucose, insulin and GLP-1 concentrations and one for the glucose metabolism in the gut, to represents their variations in the subject's body.

In the present study, we have mathematically investigated the impact of vildagliptin as an add-on to metformin to regulate the blood sugar of type 2 diabetic subjects. The drugs pharmacokinetics is modeled by combining the models proposed by Lin et al. (the updated Stepensky et al. model) and Landersdorfer et al. To model the drugs pharmacodynamics, simple mathematical models with minimal number of compartments cannot be utilized since they cannot accommodate the required compartments to represent the pharmacodynamics of vildagliptin and metformin at the same time. Therefore, a comprehensive mathematical model developed in our previous work for a group of type 2 diabetic subjects [Vahidi, Kwok, Gopaluni et al. (2016)] is used and the rate of various species in different organs (i.e. glucose, insulin and GLP-1) are modified to account for the effects attributed to the drugs. Computer simulations are performed to investigate the impact of the vildagliptin and metformin on blood sugar regulation when are used individually and combinedly.
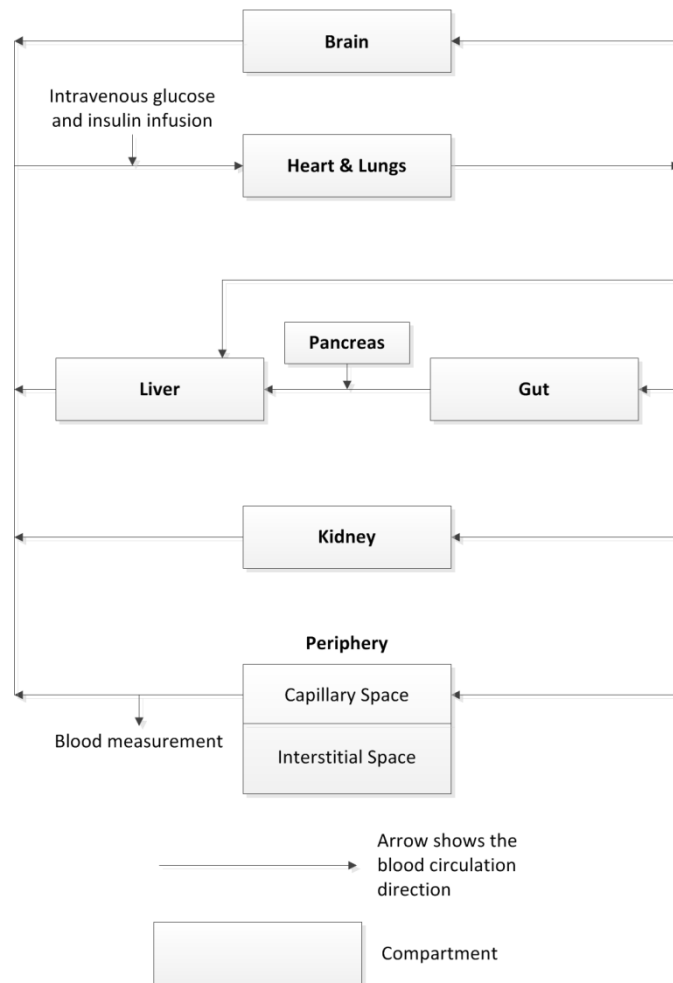
2 Mathematical modeling

2.1 Vahidi et al. model

Vahidi et al. model is a detailed mathematical model proposed for healthy and type 2 diabetic subjects which considers the insulin, glucagon and incretins hormonal regulatory effects on glucose [Vahidi, Kwok, Gopaluni et al. (2016)]. The model is an expanded form of another model proposed by Vahidi et al. [Vahidi, Kwok, Gopaluni et al. (2011)] for type 2 diabetic subjects based on a detailed model previously developed by Sorensen for healthy subjects [Sorensen (1985)]. This model is used to investigate the drugs pharmacodynamics.

The model has four sub-models representing different substance concentrations, one of which for the blood glucose concentration and three of which for the concentrations of glucose regulatory hormones including insulin, glucagon and incretins in the body. Different number of compartments is considered for each sub-model. The insulin sub-model comprises seven compartments interconnected by main blood vessels as depicted in Fig 1. The same compartments are considered for the glucose sub-model except for the pancreas compartment not included into the glucose sub-model as an individual compartment. For the incretins and glucagon, the whole body is considered as one compartment. For some compartments, sub-compartments are considered to account for the remarkable species transport resistance between the capillaries and interstitial fluid space (e.g. peripheral compartment in insulin sub-model as shown if Fig. 1) [Sorensen (1985)]. Mass balance over each sub-compartment constitutes the mathematical model equations (Appendix A). The Vahidi et al. model structure for healthy and type 2 diabetic subjects are the same. Only the values for model parameters are different. For the present study, the parameters for type 2 diabetic subjects are used and are available in Appendix A.

It should be noted that since GLP-1 is the only functional incretins in type 2 diabetic subjects [Garber (2011); Kim and Egan (2008); Meier and Nauck (2010)] and Vahidi et al. has considered both GLP-1 and GIP (another one of the two most important incretin hormones) concentrations in their model, a simple modification is implemented in Vahidi

et al. model and instead of incretins concentration only GLP-1 concentration is considered.

Figure 1: Schematic representation of the insulin sub-model

2.2 Drugs pharmacokinetics modeling

The pharmacokinetics of metformin together with vildagliptin is modeled by combining the Lin et al. and Landersdorfer et al. PK mathematical models. Based on the metformin mechanism of action which triggers hepatic glucose production and peripheral and GI glucose uptakes, three compartments were considered to model metformin pharmacokinetics. Using the same approach here, we use the Lin et al. model to calculate the metformin concentration in the liver, GI tract and peripheral tissues. The calculated concentrations are used in the PD model to obtain the metformin glucose lowering effect on those specific organs.

The Landersdorfer et al. [Landersdorfer, He and Jusko (2012a)] PK/PD model for vildagliptin, considers the drug distribution and elimination into two central and peripheral compartments. In these compartments, the drug binds to the active DPP-4 enzyme and deactivates it causing the increase in active GLP-1 presence into the circulation which consequently decreases the blood sugar. The drug concentration in central compartment is used to calculate the drug effect in the PD model.

2.3 Drugs pharmacodynamics modeling

Stepensky et al. employed indirect response modeling approach to model the metformin pharmacodynamics. They defined three variables, one of which for the inhibition effect of metformin on hepatic glucose production and two of which for the stimulation effect of metformin on GI and peripheral glucose uptake and used them in metformin PD model. In another attempt for metformin pharmacodynamics modeling, Sun et al. [Sun, Kwok, Gopaluni et al. (2011)] utilized the variables defined by Stepensky et al. and modified the hepatic glucose production rate and GI and peripheral glucose uptake rates defined in Vahidi et al. first model [Vahidi, Kwok, Gopaluni et al. (2011)] to address the metformin glucose lowering effect. Here, we have considered the similar approach in modeling the metformin pharmacodynamics by modifying the metabolic rates in the Vahidi et al. expanded model [Vahidi, Kwok, Gopaluni et al. (2016)]. The sigmoidal E_{max} model is used to define the variables attributed to inhibition of hepatic glucose production and stimulation of GI and peripheral glucose uptake rates as follows [Sun, Kwok, Gopaluni et al. (2011)]:

$$E_L = \frac{E_{Lmax}(A_L)^{nL}}{(A_{L50})^{nL}+(A_L)^{nL}} \tag{1}$$

$$E_G = \frac{E_{Gmax}(A_G)^{nG}}{(A_{G50})^{nG}+(A_G)^{nG}} \tag{2}$$

$$E_P = \frac{E_{Pmax}(A_P)^{nP}}{(A_{P50})^{nP}+(A_P)^{nP}} \tag{3}$$

where E_L, E_G and E_P are the metformin inhibitory and stimulatory effects at their corresponding metformin concentrations (i.e. A_L, A_G and A_P) in liver, gut and periphery compartments, respectively, A_{L50}, A_{G50} and A_{P50} are metformin concentrations at which half of the maximum effect (i.e. E_{Lmax}, E_{Gmax} and E_{Pmax}) is obtained. Using Eqs. (1-3), A.11, A.12 and A.16, the modified rates of the Vahidi et al. model are:

$$r_{HGP}^m = r_{HGP}(1 - E_L) \tag{4}$$

$$r_{GGU}^m = r_{GGU}(1 + E_G) \tag{5}$$

$$r_{PGU}^m = r_{PGU}(1 + E_P) \tag{6}$$

According to the vildagliptin mechanism of action which deactivates the active DPP-4 enzyme, the PD model of vildagliptin is formulated by modifying Eq. (A.54) as follows:

$$V^{\Psi_1}\frac{d\Psi_1}{dt} = r_{I\Psi_1 P} - [K_{out} + (R_{maxC} - DR_C) \times Cf_2] \times \Psi_1 \tag{7}$$

where $r_{I\Psi_1 P}$ is the rate of GLP-1 secretion calculated by Eq. (A.53), K_{out} is the first order clearance rate constant from the blood circulation for GLP-1 cleared through a non-

saturable pathway independent on the DPP-4 concentration and $(R_{maxC} - DR_C) \times Cf_2$ is the saturable DPP-4 eliminating pathway where DR_C is the drug deactivated DPP-4 concentration at central compartment and R_{maxC} is the maximum available active DPP-4 concentration at zero drug concentration [Landersdorfer, He and Jusko (2012a)]. The numerical values of K_{out} and Cf_2 constants are set such that their values at zero drug concentration equals the Vahidi et al. model and their ratio equals to that of the Landersdorfer et al. model. The rest of the PD model parameters are taken from [Landersdorfer, He and Jusko (2012a); Sun, Kwok, Gopaluni et al. (2011); Vahidi, Kwok, Gopaluni et al. (2016)].

3 Results and discussion

3.1 Steady states solution

The resulted PK/PD mathematical model for metformin and vildagliptin comprises 37 ordinary differential equations (ODEs), 27 equations for the modified Vahidi et al. model, 6 equations for Landersdorfer et al. PK model and 4 equations for the Lin et al. PK model as well as many algebraic equations to be solved alongside the ODEs. The initial conditions of the ODEs are obtained by solving the model at steady states. Fasting condition with no drug administration is considered as the steady states for the diabetic subjects. Therefore, the initial conditions for the Lin et al. and Landersdorfer et al. PK model equations are zero for all equations. To obtain the initial conditions for modified Vahidi et al. model equations, all derivative terms are set to zero and all metabolic rates are set at their basal conditions (i.e. fasting condition) resulting in four decoupled sets of algebraic equations corresponding to each sub-model. At fasting conditions, since no glucose is present in the gut, the initial condition for GLP-1 sub-model is zero since this hormone is secreted when glucose is present into the duodenum. For glucagon sub-model, since normalized value of glucagon is used, an arbitrary value is considered for glucagon basal concentration. For glucose sub-model, the degree of freedom for algebraic solution is one and one unknown variable has to be set and therefore, the available measured value of peripheral glucose concentration is set at 153.4 mg/dl. Similar to the glucose sub-model, the available measured peripheral insulin concentration is set at 5.9 mU/l. These values are taken from the clinical data sets published by Knop et al. [Knop, Vilsboll, Hojberg et al. (2007)] which were used by Vahidi et al. to estimate their model parameters for the group of diabetic subjects.

3.1 Dynamic solution

To investigate the lowering effect of drug administration on type 2 diabetic subjects, an *in silico* 50 g oral glucose tolerance test (OGTT) with the administration of 500 mg metformin together with 25 mg vildagliptin is performed. The test is repeated with the administration of individual drugs and with no drug administration. Fig. 2 shows the variations of peripheral glucose concentrations and Fig. 3 (a) and (b) indicate the variations of peripheral insulin and GLP-1 concentrations during the four 50 g OGTTs.
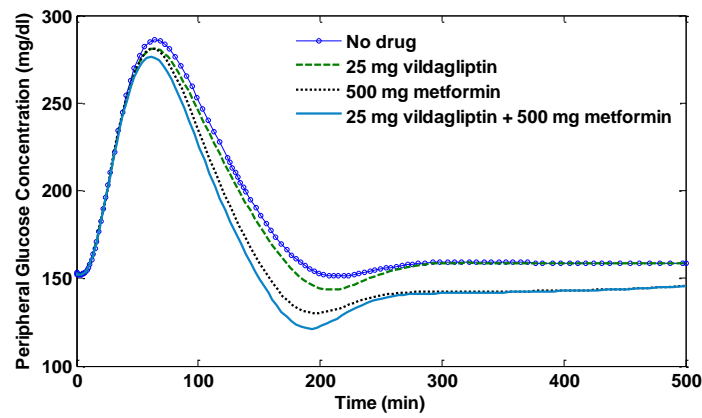
Figure 2: The variations of peripheral glucose concentration during the 50 g OGTT
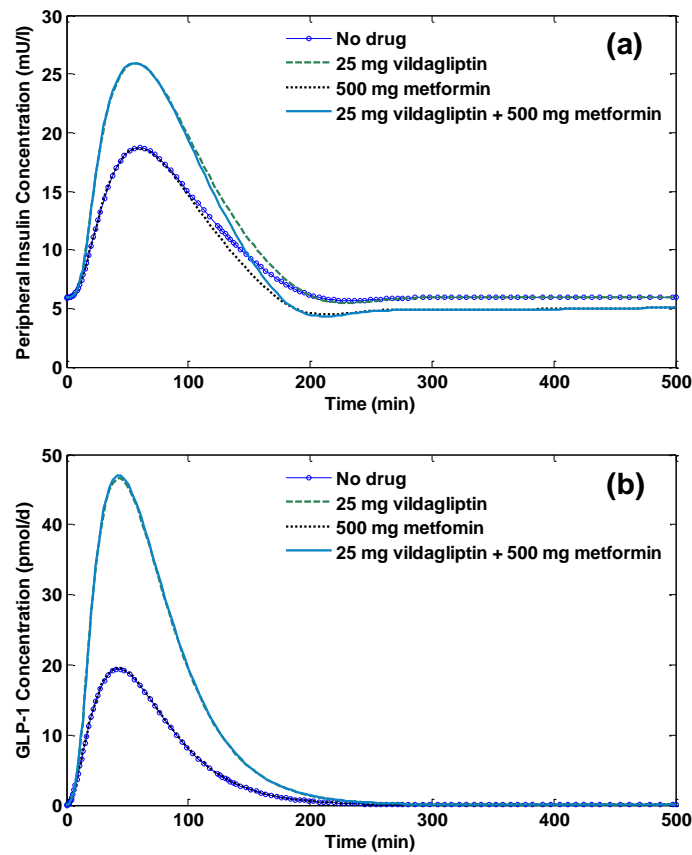
Figure 3: The variations of peripheral insulin and GLP-1 concentration during the 50 g OGTT

As Fig. 2 indicates, vildagliptin reveals a non-significant lowering effect on the blood glucose levels. According to Fig. 3 (b), vildagliptin has effectively increased the GLP-1 level by inhibiting the DPP-4 enzyme and consequently, the plasma insulin concentration has a remarkable increment (Fig. 3 (a)), however, due to the high insulin resistance and significant abnormalities associated with this group of diabetic subjects, the impact of insulin increase on lowering the blood glucose is not significant. As the time passes, vildagliptin gets cleared from the circulation and therefore, its effect completely disappears after around 300 min of the test.

On the other hand, although metformin reveals a weak impact on lowering the blood sugar at the beginning of the test, its glucose lowering effect increases as the blood sugar level falls. The reason is due to the high suppression of hepatic glucose production when the blood sugar is high. Hepatic glucose production is inversely proportional to the blood glucose concentration and its amount is significantly reduced by high levels of plasma glucose concentration at the beginning of the test (see Fig. 4). Since the glucose lowering effect of metformin is remarkably implemented by suppressing the hepatic glucose production, metformin becomes almost ineffective on the liver when hepatic glucose production is already suppressed by other factors. As the results indicate, the glucose lowering effect of metformin lasts longer than that of vildagliptin for this group of diabetic subjects. It also diminishes gradually by passage of time until it fully vanishes at around 1000 min of the test (the results are not shown).
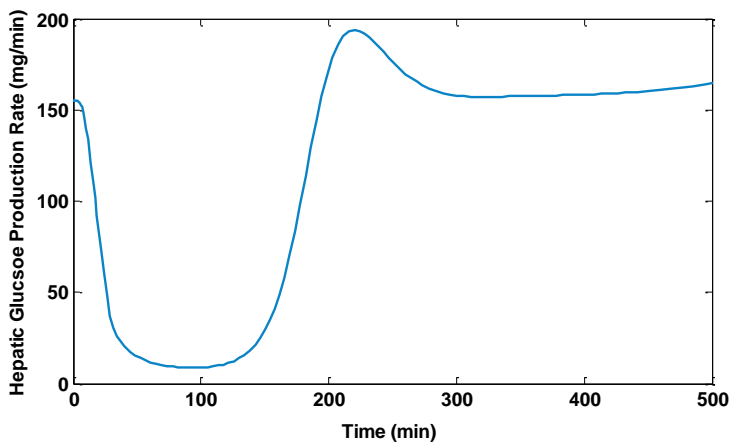

Figure 4: The variations of hepatic glucose production rate during the 50 g OGTT with the administration of 500 mg metformin

The results also prove the drugs complementation of each other's action. Vildagliptin complements the glucose lowering effect of metformin since their mechanisms of action do not interfere and therefore, the vildagliptin glucose lowering effect adds to that of metformin.

Quantitative comparisons between the four *in silico* tests are provided in Fig. 5-8. The information on these figures (except for Fig. 8) are obtained by integrating the production and uptake rates of glucose and insulin for the four oral glucose tolerance tests up to 300

min where the species concentrations reach almost to their steady state values (see Figs. 2 and 3). Fig. 8 indicates the integration of glucose concentration profiles (Fig. 2) for 300 min of the tests with drug administration subtracted from the same amount obtained from the test with no drug administration.
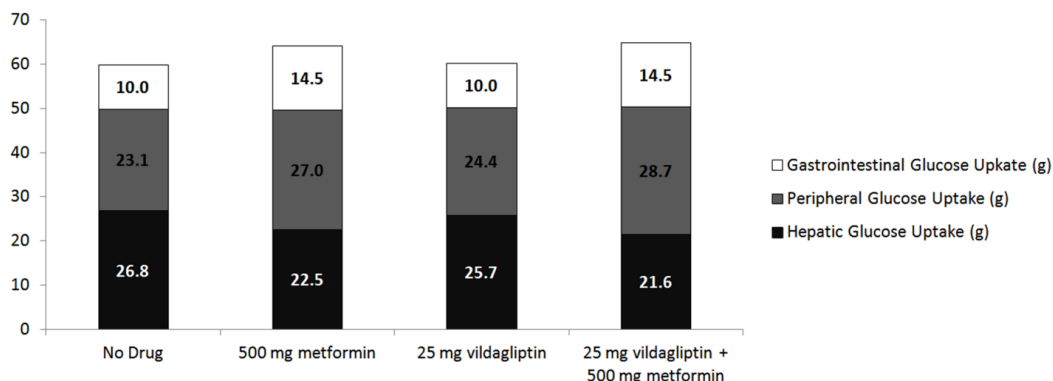
Figure 5: Total hepatic, peripheral and GI glucose uptake amounts for 300 min of the four 50 g oral glucose tolerance tests
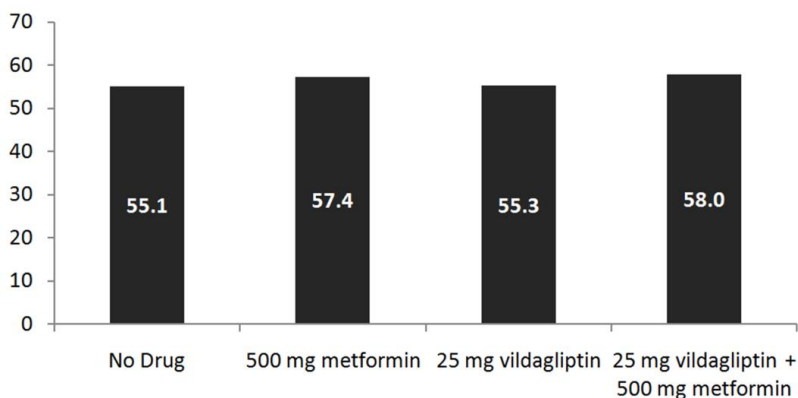

Figure 6: Total hepatic glucose production amount (g) for 300 min of the four 50 g oral glucose tolerance tests

As Fig. 5 indicates, total peripheral and GI glucose uptake amounts are enhanced by approximately 17.5% and 45.5%, respectively, for the tests with metformin administration compared to the tests with no metformin administration, however, in contrary to the expectations, the total hepatic glucose production amount is apparently not only suppressed after metformin administration, but also slightly augmented by approximately 4.5% (see Fig. 6). As implied earlier, glucose induced suppression of hepatic glucose production is not abnormal for this group of diabetic subjects causing the significant suppression of hepatic glucose production rate when glucose concentration is high. Since the glucose levels during the OGTT tests are remarkably higher when no

metformin is administered compared with the tests with metformin administration (see Fig. 2), it yields significantly higher suppression of hepatic glucose production. Therefore, the reason for slightly more total hepatic glucose production amount is due to the remarkably lower glucose levels. Moreover, a more realistic evaluation of metformin suppressive effect on hepatic glucose production should be performed using Eq. (4) by calculating the suppression percentage based on r_{HGP} and r_{HGP}^m values which results in approximately 35% of hepatic glucose production suppression.

As Fig. 7 indicates, vildagliptin administration enhances the total pancreatic insulin secretion amount by approximately 17.5%. Also, when metformin is administered, the total pancreatic insulin secretion is lowered due to the lowered glucose levels caused by the administration of metformin which consequently lowers the need of pancreatic insulin secretion.
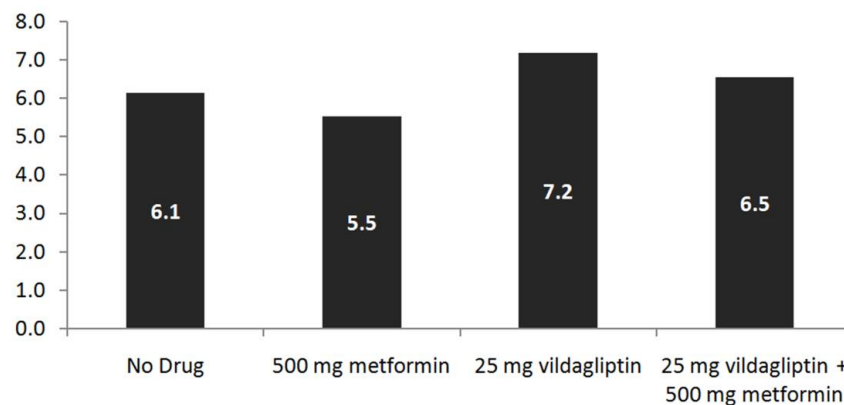
Figure 7: Total pancreatic insulin secretion amount (U) for 300 min of the four 50 g oral glucose tolerance tests

Integration of glucose concentration profile for the tests with drug administration enables a quantitative comparison of drugs lowering effect on blood glucose levels. As Fig. 8 shows, the glucose lowering effect of metformin is much stronger than that of vildagliptin. Nevertheless, something more interesting is that the glucose lowering effect of the combined drugs is higher than the summation of individual drugs' effects proving the synergetic complementation of combined drugs. This is because of the different drugs mechanisms of action in lowering the blood sugar level which not only interfere each other's action, but also amplify each other's action.
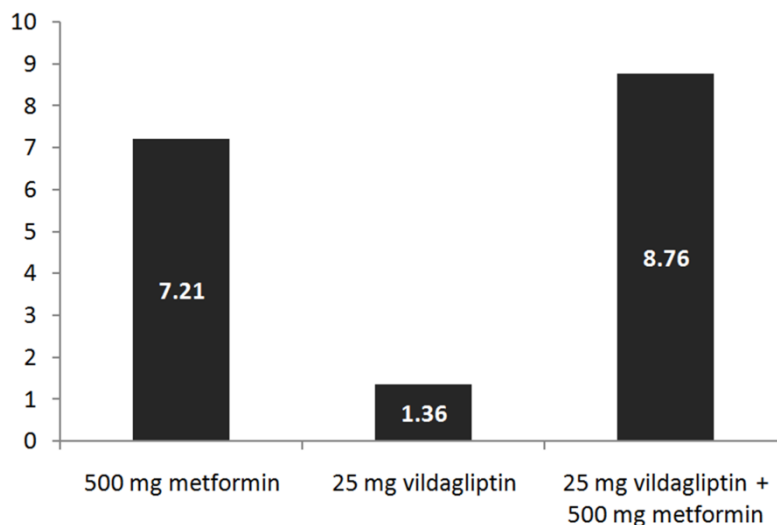
Figure 8: Integration of glucose concentration profiles for the tests with drugs administration subtracted from the same value obtained from the test with no drug administration. The unit of the indicated values are min.g/dl

3 Conclusion

We developed a mathematical PK/PD model for the administration of vildagliptin as an add-on to metformin by combining the available mathematical models individually proposed for metformin and vildagliptin. For the PK model, Lin et al. PK model for metformin and Landersdorfer et al. PK model for vildagliptin were used and for the PD model a comprehensive mathematical model proposed by Vahidi et al. for type 2 diabetic subjects with some modifications was used. The models were all interconnected to obtain the PK/PD model for the combination of vildagliptin and metformin drugs. Mathematical simulation of 50 g oral glucose tolerance test was performed and the impact of drugs administration when were used individually and combinedly was qualitatively and quantitatively investigated. Both drugs revealed glucose lowering effects. The impact of metformin on glucose level reduction was stronger than that of the vildagliptin for the group of diabetic subjects for whom the model was developed. Also, due to the separate mechanisms of action of both drugs, they synergized their glucose lowering effects which means that the glucose lowering effect of their combination was greater than the summation of their individual effects.

Appendix A

The following nomenclature is adopted for the Vahidi et al. model description:

Model variables in the glucose sub-model

D Oral glucose amount (mg)
G Glucose concentration (mg/dl)
M Multiplier of metabolic rates (dimensionless)
q Glucose amount in GI tract (mg)

Q	Vascular blood flow rate (dl/min)
r	Metabolic production or consumption rate (mg/min)
Ra	Rate of glucose appearance in the blood stream (mg/min)
T	Transcapillary diffusion time constant (min)
t	Time (min)
V	Volume (dl)

Model variables in the insulin sub-model

I	Insulin concentration (mU/l)
M	Multiplier of metabolic rates (dimensionless)
m	Labile insulin mass (U)
P	Potentiator (dimensionless)
Q	Vascular blood flow rate (l/min)
R	Inhibitor (dimensionless)
r	Metabolic production or consumption rate (mU/min)
S	Insulin secretion rate (U/min)
T	Transcapillary diffusion time constant (min)
t	Time (min)
V	Volume (l)
X	Glucose-enhanced excitation factor (dimensionless)
Y	Intermediate variable (dimensionless)

Model variables in the glucagon sub-model

Γ	Normalized glucagon concentration (dimensionless)
M	Multiplier of metabolic rates (dimensionless)
r	Metabolic production or consumption rate (dl/min)
V	Volume (dl)
t	Time (min)

Model variables in the GLP-1 sub-model

Ψ_1	GLP-1 concentration (pmol/l)
ψ_1	Amount of produced GLP-1 (pmol)
r	Metabolic production or consumption rate (pmol/min)
V	Volume (l)
t	Time (min)

First superscript

Γ	Glucagon
Ψ_1	GLP-1
B	Basal condition
G	Glucose

I   Insulin

Second superscript

∞   Final steady state value

Metabolic rate subscripts

BGU   Brain glucose uptake
GGU   Gut glucose uptake
HGP   Hepatic glucose production
HGU   Hepatic glucose uptake
$I\Psi_1 R$ Intestinal GLP-1 release
IVG   Intravenous glucose injection
IVI   Intravenous insulin injection
KGE   Kidney glucose excretion
KIC   Kidney insulin clearance
LIC   Liver insulin clearance
MΓC   Metabolic glucagon clearance
PΓC   Plasma glucagon clearance
$P\Psi_1 C$ Plasma GLP-1 clearance
PΓR   Pancreatic glucagon release
PGU   Peripheral glucose uptake
PIC   Peripheral insulin clearance
PIR   Pancreatic insulin release
RBCU Red blood cell glucose uptake

First subscripts

A   Hepatic artery
B   Brain
G   Gut
H   Heart and lungs
L   Liver
P   Periphery
S   Stomach
∞   Final steady state value

Second subscripts (if required)

C   Capillary space
F   Interstitial fluid space
l   Liquid
s   Solid

A.1 Glucose sub-model

The mass balance equation over each sub-compartment in the glucose sub-model results in the following equations:

$$V_{BC}^G \frac{dG_{BC}}{dt} = Q_B^G(G_H - G_{BC}) - \frac{V_{BF}^G}{T_B^G}(G_{BC} - G_{BF}) \tag{A.1}$$

$$V_{BF}^G \frac{dG_{BF}}{dt} = \frac{V_{BF}^G}{T_B^G}(G_{BC} - G_{BF}) - r_{BGU} \tag{A.2}$$

$$V_H^G \frac{dG_H}{dt} = Q_B^G G_{BC} + Q_L^G G_L + Q_K^G G_K + Q_P^G G_{PC} - Q_H^G G_H - r_{RBCU} + r_{IVG} \tag{A.3}$$

$$V_G^G \frac{dG_G}{dt} = Q_G^G(G_H - G_G) - r_{GGU} + Ra \tag{A.4}$$

$$V_L^G \frac{dG_L}{dt} = Q_A^G G_H + Q_G^G G_G - Q_L^G G_L + r_{HGP} - r_{HGU} \tag{A.5}$$

$$V_K^G \frac{dG_K}{dt} = Q_K^G(G_H - G_K) - r_{KGE} \tag{A.6}$$

$$V_{PC}^G \frac{dG_{PC}}{dt} = Q_P^G(G_H - G_{PC}) - \frac{V_{PF}^G}{T_P^G}(G_{PC} - G_{PF}) \tag{A.7}$$

$$V_{PF}^G \frac{dG_{PF}}{dt} = \frac{V_{PF}^G}{T_P^G}(G_{PC} - G_{PF}) - r_{PGU} \tag{A.8}$$

The metabolic rates for the glucose sub-model are summarized below:

$$r_{BGU} = 70 \tag{A.9}$$

$$r_{RBCU} = 10 \tag{A.10}$$

$$r_{GGU} = 20 \tag{A.11}$$

$$r_{PGU} = M_{PGU}^I M_{PGU}^G \, r_{PGU}^B \tag{A.12}$$

$$r_{PGU}^B = 35 \tag{A.13}$$

$$M_{PGU}^I = 1.31 + 1.22 \, tanh[0.13(I_{PF}/I_{PF}^B - 2.98)] \tag{A.14}$$

$$M_{PGU}^G = G_{PF}/G_{PF}^B \tag{A.15}$$

$$r_{HGP} = M_{HGP}^I M_{HGP}^G \, M_{HGP}^\Gamma \, r_{HGP}^B \tag{A.16}$$

$$r_{HGP}^B = 35 \tag{A.17}$$

$$\frac{d}{dt} M_{HGP}^I = 0.04(M_{HGP}^{I\infty} - M_{HGP}^I) \tag{A.18}$$

$$M_{HGP}^{I\infty} = 1.836 - 1.73 \, tanh[1.46(I_L/I_L^B - 0.64)] \tag{A.19}$$

$$M_{HGP}^G = 1.29 - 0.91 \, tanh[0.48(G_L/G_L^B - 0.301)] \tag{A.20}$$

$$M_{HGP}^\Gamma = 2.7 \, tanh[0.39 \, \Gamma/\Gamma^B] - f \tag{A.21}$$

$$\frac{d}{dt} f = 0.0154[\left(\frac{2.7 \, tanh[0.39\Gamma/\Gamma^B]-1}{2}\right) - f] \tag{A.22}$$

$$r_{HGU} = M_{HGU}^I M_{HGU}^G \, r_{HGU}^B \tag{A.23}$$

$$r_{HGU}^B = 20 \tag{A.24}$$

$$\frac{d}{dt} M_{HGU}^I = 0.04(M_{HGU}^{I\infty} - M_{HGU}^I) \tag{A.25}$$

$$M_{HGU}^{I\infty} = 0.125 + 0.94 \, tanh[1.73(I_L/I_L^B - 0.039)] \tag{A.26}$$

$$M_{HGU}^G = 6.88 + 6.876 \, tanh[2.24(G_L/G_L^B - 1.57)] \tag{A.27}$$

$$r_{KGE} = 71 + 71 \, tanh[0.11(G_K - 460)] \quad 0 \leq G_K < 460$$
$$\tag{A.28}$$
$$r_{KGE} = -330 + 0.872G_K \qquad\qquad G_K \geq 460$$

The glucose absorption amount in the GI tract, *Ra*, is calculated from the following equations:

$$\frac{dq_{Ss}}{dt} = -0.074q_{Ss} + D\delta(t) \tag{A.29}$$

$$\frac{dq_{Sl}}{dt} = -k_{empt}q_{Sl} + 0.074q_{Ss} \tag{A.30}$$

$$\frac{dq_{int}}{dt} = -0.078q_{int} + k_{empt}q_{Sl} \tag{A.31}$$

$$k_{empt} = \frac{0.0434}{2}\{tanh[\varphi_1(q_{Ss} + q_{Sl} - 0.82D)]$$
$$- tanh[\varphi_2(q_{Ss} + q_{Sl} - 0.00236D)] + 2\} \tag{A.32}$$

$$\varphi_1 = \frac{5}{2D(1-0.82)} \tag{A.33}$$

$$\varphi_2 = \frac{5}{0.0047D} \tag{A.34}$$

$$Ra = 0.0698q_{int} \tag{A.35}$$

where $\delta(t)$ is the impulse function.

A.2 Insulin sub-model

The mass balance over the sub-compartments of the insulin sub-model is as follows:

$$V_B^I \frac{dI_B}{dt} = Q_B^I(I_H - I_B) \tag{A.36}$$

$$V_H^I \frac{dI_H}{dt} = Q_B^I I_B + Q_L^I I_L + Q_K^I I_K + Q_P^I I_{PV} - Q_H^I I_H \tag{A.37}$$

$$V_G^I \frac{dI_G}{dt} = Q_G^I(I_H - I_G) \tag{A.38}$$

$$V_L^I \frac{dI_L}{dt} = Q_A^I I_H + Q_G^I I_G - Q_L^I I_L + r_{PIR} - r_{LIC} + r_{IVI} \tag{A.39}$$

$$V_K^I \frac{dI_K}{dt} = Q_K^I(I_H - I_K) - r_{KIC} \tag{A.40}$$

$$V_{PC}^I \frac{dI_{PC}}{dt} = Q_P^I(I_H - I_{PC}) - \frac{V_{PF}^I}{T_P^I}(I_{PC} - I_{PF}) \tag{A.41}$$

$$V_{PF}^I \frac{dI_{PF}}{dt} = \frac{V_{PF}^I}{T_P^I}(I_{PC} - I_{PF}) - r_{PIC} \tag{A.42}$$

The metabolic rates for the insulin sub-model are:

$$r_{LIC} = 0.4[Q_A^I I_H + Q_G^I I_G + r_{PIR}] \tag{A.43}$$

$$r_{KIC} = 0.3Q_K^I I_K \tag{A.44}$$

$$r_{PIC} = \frac{I_{PF}}{[\left(\frac{1-0.15}{0.15Q_P^I}\right) - \frac{20}{V_{PF}^I}]}$$

(A.45)

A separate model is included into the Vahidi et al. model to calculate the pancreatic insulin secretion rate under the insulin sub-model [Vahidi, Kwok, Gopaluni et al. (2016)] whose equations are not shown here.

A.3 Glucagon sub-model

Since the glucagon sub-model considers the whole body as one compartment, it only has one equation:

$$V^\Gamma \frac{d\Gamma}{dt} = r_{P\Gamma R} - r_{P\Gamma C}$$

(A.46)

The metabolic rates for the glucagon sub-model are summarized below:

$$r_{P\Gamma C} = 9.1\Gamma$$

(A.47)

$$r_{P\Gamma R} = M_{P\Gamma R}^G M_{P\Gamma R}^I r_{P\Gamma R}^B$$

(A.48)

$$M_{P\Gamma R}^G = 1.31 - 0.61 tanh[1.06(G_H/G_H^B - 0.47)]$$

(A.49)

$$M_{P\Gamma R}^I = 2.93 - 2.09 tanh[4.18(I_H/I_H^B - 0.62)]$$

(A.50)

$$r_{P\Gamma R}^B = 9.1$$

(A.51)

A.4 GLP-1 sub-model

The GLP-1 sub-model also has one compartment, however, two equations are used to model this sub-model [Vahidi, Kwok, Gopaluni et al. (2016)]. As mentioned, this sub-model was originally for incretins (i.e. GLP-1 and GIP together), but since GLP-1 is the only functional incretins for type 2 diabetic subjects, the Vahidi et al. model is slightly modified to only accommodate the GLP-1. For that, only the constants are changed and the sub-model structure is remained unchanged:

$$\frac{d\psi_1}{dt} = 8.248k_{empt}q_{Sl} - r_{I\psi_1 P}$$

(A.52)

$$r_{I\psi_1 P} = \frac{\psi_1}{35.1}$$

(A.53)

$$V^{\Psi_1} \frac{d\Psi_1}{dt} = r_{I\psi_1 P} - r_{P\psi_1 C}$$

(A.54)

The model constant parameters are available in [Vahidi, Kwok, Gopaluni et al. (2016)].

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