

A Model of Glucose-Insulin-Pramlintide Pharmacokinetics and Pharmacodynamics in Type I Diabetes

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Abstract

Type I diabetes mellitus (T1DM) complications are significantly reduced when normoglycemic levels are maintained via intensive therapy. The artificial pancreas is designed for intensive glycemic control; however, large postprandial excursions after a meal result in poor glucose regulation. Pramlintide, a synthetic analog of the hormone amylin, reduces the severity of postprandial excursions by reducing appetite, suppressing glucagon release, and slowing the rate of gastric emptying. The goal of this study is to create a glucose-insulin-pramlintide physiological model that can be employed into a controller to improve current control approaches used in the artificial pancreas. A model of subcutaneous (SC) pramlintide pharmacokinetics (PK) was developed by revising an intravenous (IV) pramlintide PK model and adapting SC insulin PK from a glucose-insulin model. Gray-box modeling and least squares optimization were used to obtain parameter estimates. Pharmacodynamics (PD) were obtained by choosing parameters most applicable to pramlintide mechanisms and then testing using a proportional PD effect using least squares optimization. The model was fit and validated using 27 data sets, which included placebo, PK, and PD data. SC pramlintide PK root mean square error values range from 1.98 to 10.66 pmol/L. Pramlintide PD RMSE values range from 10.48 to 42.76 mg/dL. A new *in silico* model of the glucose-insulin-pramlintide regulatory system is presented. This model can be used as a platform to optimize dosing of both pramlintide and insulin as a combined therapy for glycemic regulation, and in the development of an artificial pancreas as the kernel for a model-based controller.

Keywords

artificial pancreas, physiology model, type I diabetes mellitus, pramlintide, postprandial hyperglycemia

Type 1 diabetes mellitus (T1DM) is a chronic metabolic disorder characterized as an autoimmune disease in which the body specifically attacks pancreatic β -cells. This results in insulin and amylin deficiencies, which produces chronic hyperglycemia.¹ Insulin injection therapy is effective in many patients, but it is imperfect. People with T1DM face a trade-off among glycemic control, lifestyle flexibility, and therapy effort. Using current therapy options, near normoglycemia can be achieved only by patients at the expense of lifestyle flexibility and increased therapy effort. Because of this excellent glycemic control remains more of an aspiration than a reality.

Recent technological advances provide an opportunity to combine 3 technologies: continuous glucose monitors, insulin pumps, and a control algorithm; this forms the basis of an artificial pancreas.^{2–5} Despite important advances in the artificial pancreas, most patients with T1DM are still unable to achieve near-normoglycemia with insulin therapy alone. The limitations of current insulin replacement therapy are especially evident during the postprandial period, when rapid and profound changes in glucose flux occur as a sudden appearance of meal-derived glucose goes into circulation.^{6–8}

In the development of an artificial pancreas, the primary difficulties are the inherent time delays in the closed system due to subcutaneous (SC) delivery of insulin and SC reading of glucose, with additional built-in filters in the monitor.² The lack of timely information coupled with large postprandial excursions after a meal and poor insulin management make glucose regulation very difficult.^{2,8} Postprandial glucose control is the 1 area where the largest gain can be achieved; therefore, the focus is on finding methodologies to lower postprandial glucose excursions.

In healthy individuals, insulin and amylin are cosecreted from the pancreatic β -cells in response to a meal.⁹ Insulin acts to inhibit hepatic glucose output through inhibition of

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glucagon from the pancreatic α -cells and stimulates the uptake of glucose into peripheral insulin-sensitive cells. Amylin modulates appetite, suppresses glucagon secretion, and slows the rate at which nutrients are delivered from the stomach to the small intestine for absorption. Amylin mitigates the influx of endogenous and exogenous glucose into the circulation and thus improves the rate of glucose clearance incurred by insulin.^{10,11}

In T1DM however, both amylin and insulin production are decreased significantly due to the death of β -cells. Patients exhibit a paradoxical postprandial hyperglucagonemia in which endogenous glucagon levels are elevated in the portal circulation and insulin levels are reduced. Administration of exogenous insulin alone does not normalize the portal glucagon to insulin ratio; the liver continues to release glucose into the circulation, resulting in hyperglycemia.¹² It seems logical then to include both insulin and amylin in the fight against postprandial hyperglycemia in T1DM. Pramlintide, a soluble, nonaggregating, equipotent synthetic analog of amylin, is approved by the FDA and used to treat T1DM patients who are unable to obtain near-normoglycemia with insulin therapy alone.¹³

In 2012, a study was done using closed-loop control of insulin along with pramlintide treatment in young adults and adolescents, who demonstrated marked improvements in regulation and significant reduction in glucose postprandial peak and a delay of peak glucose occurring more than 1 hour later than the placebo patients.¹⁴ The meal's immediate impact is lowered dramatically and spread out making glucose control much improved.¹⁴ The controller was a proportional integral derivative (PID) controller using model-based insulin feedback.¹⁵ Results looked very promising but were essentially preliminary with only 8 patients.

In the closed-loop study above,¹⁴ there were no incidents of hypoglycemia over the 2 days. Weinzimer et al¹⁴ gave no premeal boluses to the patients. All insulin delivery was due to automatic feedback based on actual glucose readings. Many other studies¹⁶⁻²³ have reported that pramlintide resulted in hypoglycemia. However, the cause of hypoglycemia was a result of the interplay between insulin and pramlintide. These studies when exploring pramlintide dosing did not investigate lower insulin dosages. Pramlintide mechanisms allow for postprandial glucose to be significantly reduced, thus requiring a lower insulin dosage than previously used. What is required is a better model to help calculate new premeal boluses in the presence of pramlintide, test other dose regimens, and test the possibility of use in a better model-based controller.

The most detailed model for pharmacokinetics and pharmacodynamics (PK/PD) for pramlintide¹³ is based on using intravenous (IV) pramlintide doses. The most recent model²⁴ had PD based on 1 set of 15 patients using 1 concentration of SC pramlintide given at only 1 time point relative to a single meal and insulin bolus. The model did not include PK of pramlintide but instead had parameters for the gastric

emptying model modified proportionately by initial dosage of pramlintide and amount of glucose present in the meal.²⁴

The study presented in this article was undertaken to develop a PK/PD model based on an existing glucose-insulin model²⁵ with the addition of the drug pramlintide. This model is based on SC lispro (short-acting) insulin²⁶ and pramlintide administration along with a working meal model. Pramlintide PD was based on the mechanisms of pramlintide and its effect on plasma glucose at the postprandial period. Parameter fits and model validation were achieved using data found in the literature, which includes 6 articles with 27 data sets.^{7,13,17,21-23} We sought to create a glucose-insulin-pramlintide model that could be used to evaluate strategies incorporating pramlintide into T1DM therapies.

Model

The proposed model is based on parameters and equations from 3 articles.^{20,25-26} This model consists of a glucose-regulatory and insulin action subsystem model²⁵ with SC lispro (short-acting) insulin kinetics (insulin subsystem)²⁶ substituted. The pramlintide PK is taken from a previous study²⁰ with the SC pramlintide PK adapted from SC insulin PK.²⁶

Several changes to the original models^{20,25-26} have been made. A meal correction, a change in $t_{\max,G}$, and the addition of a meal delay (n_0) all in the presence of pramlintide have been added to the glucose-regulatory subsystem found in Hovorka et al²⁵. The insulin action subsystem of Hovorka et al²⁵ and the lispro (short-acting) insulin SC kinetics of Wilinska et al²⁶ both remain unchanged. Clodi et al²⁰ has been converted from IV pramlintide administration to SC by the addition of a SC compartment (SQ_{pf}). A pramlintide transport delay (p_0), which is the delay from the time pramlintide is administered to the time an effect of pramlintide is seen on blood glucose has also been added. The model outline is shown in Figure 1.

Glucose Subsystem

The first 2 states are the total mass of glucose in each compartment, scaled by the patient weight.²⁵ The material balance around the first compartment includes renal clearance (F_R), glucose infusion (u_G), and endogenous glucose production (EGP) (which is constrained to be positive),

$$\frac{dG_1}{dt} = - \left[\frac{F_{01}^c}{V_G G} + I_1 \right] G_1 + k_g G_2 - F_R + u_G + EGP \quad (1)$$

$$EGP = \begin{cases} EGP_0 (1 - I_3) & \text{if } EGP \geq 0 \\ 0 & \text{otherwise} \end{cases}$$

$$\frac{dG_2}{dt} = I_1 G_1 - (k_g + I_2) G_2 \quad (2)$$

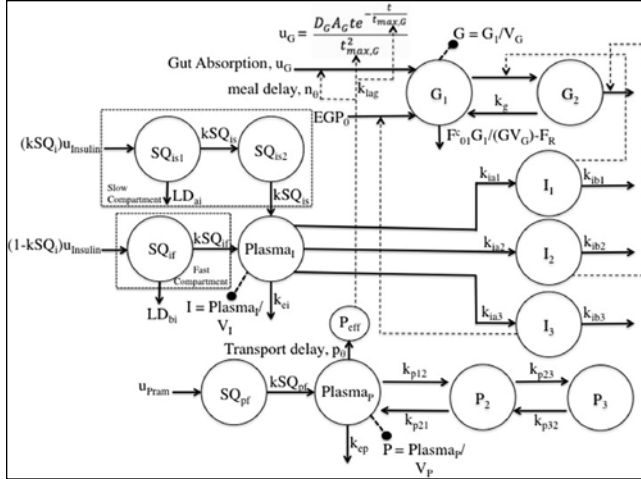


Figure 1. Compartment model of glucose–insulin–pramlintide system. G_1 and G_2 represent masses in accessible (plasma) and non-accessible compartments, $Plasma_i$ represents plasma insulin; I_i represents insulin action on glucose transport, disposal, and endogenous glucose production; $Plasma_p$ represents plasma pramlintide; P_i represents hypothetical compartments that affect $Plasma_p$; P_{eff} represents the effective pramlintide compartment that is used for pramlintide mechanisms on glucose. For more details, see the text.

$$G = \frac{G_1}{V_G} \quad (3)$$

where G_1 and G_2 represent the masses of glucose in the accessible (where measurements are made) and non-accessible compartments, k_g represents the transfer rate constant from the non-accessible to the accessible compartment, V_G represents the distribution volume of the accessible compartment, G is the (measurable) glucose concentration (mmol/L), and EGP_0 represents endogenous glucose production EGP extrapolated to the zero insulin concentration.

F_{01}^c is the total non-insulin-dependent glucose flux corrected for the ambient glucose concentration

$$F_{01}^c = \begin{cases} F_{01} & \text{if } G \geq 4.5 \text{ mmol L}^{-1} \\ \frac{F_{01}G}{4.5} & \text{otherwise.} \end{cases} \quad (4)$$

F_R is the renal glucose clearance above the glucose threshold of 9 mmol L⁻¹

$$F_R = \begin{cases} 0.003(G-9)V_G & \text{if } G \geq 9 \text{ mmol L}^{-1} \\ 0 & \text{otherwise.} \end{cases} \quad (5)$$

A second order pulse response is used as the meal disturbance,²⁵

$$u_G = \frac{D_G A_G t e^{-\frac{t}{t_{max,G}}}}{t_{max,G}^2} \quad \text{if pramlintide} = 0 \quad (6)$$

where $t_{max,G}$ is the time-of-maximum appearance rate of glucose in the accessible glucose compartment, D_G is the amount of carbohydrates digested, and A_G is carbohydrate bioavailability.

Insulin Subsystem

SC lispro (short-acting) insulin PK,²⁶

$$\frac{dSQ_{is1}}{dt} = kSQ_i u_{Insulin} - kSQ_{is} SQ_{is1} - LD_{ai} \quad (7)$$

$$\frac{dSQ_{if}}{dt} = (1 - kSQ_i) u_{Insulin} - kSQ_{if} SQ_{if} - LD_{bi} \quad (8)$$

$$\frac{dSQ_{is2}}{dt} = kSQ_{is} SQ_{is1} - kSQ_{is} SQ_{is2} \quad (9)$$

$$\frac{dPlasma_i}{dt} = kSQ_{is} SQ_{is2} + kSQ_{if} SQ_{if} - k_{ei} Plasma_i \quad (10)$$

$$I = \frac{Plasma_i}{V_I} \quad (11)$$

where the insulin dosage is represented by $u_{Insulin}$, the elimination rate constant is k_{ei} , $Plasma_i$ is the measurable insulin compartment, and kSQ_{is1} , kSQ_{is2} , and kSQ_{if} are rate constants of the slow and fast compartments, respectively. LD_{ai} and LD_{bi} represent Michaelis Menten degradation kinetics of insulin. I is the (measurable) plasma insulin concentration in mU/L.

$$LD_{ai} = \frac{V_{max,LD} SQ_{is1}}{k_{M,LD} + SQ_{is1}} \quad (12)$$

$$LD_{bi} = \frac{V_{max,LD} SQ_{if}}{k_{M,LD} + SQ_{if}} \quad (13)$$

Insulin Action Subsystem

The model represents 3 actions of insulin on glucose kinetics,²⁵

$$\frac{dI_1}{dt} = -k_{ia1} I_1 + S_{IT} k_{ia1} I \quad (14)$$

$$\frac{dI_2}{dt} = -k_{ia2} I_2 + S_{IT} k_{ia2} I \quad (15)$$

$$\frac{dI_3}{dt} = -k_{ia3}I_3 + S_{IE}k_{ia3}I \quad (16)$$

where I_1 , I_2 , and I_3 represent the (remote) effects of insulin on glucose distribution/transport, glucose disposal, and endogenous glucose production;²⁵ k_{ia1} , k_{ia2} , and k_{ia3} represent deactivation rate constants, and $S_{IT}k_{ia1}$, $S_{IT}k_{ia2}$, and $S_{IE}k_{ia3}$ represent activation rate constants, which include the insulin sensitivities of distribution/transport, disposal, and EGP, respectively.

Insulin sensitivities were taken from Palerm,¹⁵ who found that nominal insulin sensitivities were generally too high for adolescents and older people (these generally result in insulin/carb ratios of 1/25 or so); these sensitivities have been reduced by one-half.¹⁵

Pramlintide Subsystem

IV pramlintide PK equations were taken from a previous pramlintide study²⁰ and adapted to SC pramlintide PK,

$$\frac{dSQ_p}{dt} = u_{Pram} - kSQ_pSQ_p \quad (17)$$

$$\frac{dPlasma_p}{dt} = kSQ_pSQ_p - (k_{ep} + k_{p21})Plasma_p + k_{p12}P_2 \quad (18)$$

$$\frac{dP_2}{dt} = k_{p21}Plasma_p - (k_{p12} + k_{p32})P_2 + k_{p23}P_3 \quad (19)$$

$$\frac{dP_3}{dt} = k_{p32}P_2 - k_{p23}P_3 \quad (20)$$

$$P = \frac{Plasma_p}{V_p} \quad (21)$$

$$P_{eff} = \begin{cases} 0 & 0 \leq t \leq p_\theta \\ P(t - p_\theta) & t > p_\theta \end{cases} \quad (22)$$

where the pramlintide dosage is represented by u_{Pram} , the elimination rate constant is k_{ep} , $Plasma_p$ is the measurable pramlintide compartment, kSQ_p is a rate constant, and k_{p12} , k_{p21} , k_{p23} , and k_{p32} are transfer rate constants. P_2 and P_3 represent possible effects of pramlintide on glucose. P is the (measurable) plasma pramlintide concentration in mcg/L, p_θ is a transport delay of pramlintide between its administration and its effective site resulting in an effective concentration, P_{eff}

Pramlintide Action Subsystem

Pramlintide, when in the system, affects the peak meal absorption time ($t_{max,G}$; equation 23). Changes in $t_{max,G}$ cause a shift in the meal which must be accounted for and corrected, as seen in equations 24 and 25.

$$t_{max,G,new} = t_{max,G,old} \left(1 + k_{lag} \left(P_{eff}(t) \right) \right) \quad (23)$$

$$Gap = \int_0^{t_{sw}} \frac{D_G A_G (t - n_\theta) e^{-\frac{(t-n_\theta)}{t_{max,G,old}}}}{t_{max,G,old}^2} - \int_0^{t_{sw}} \frac{D_G A_G (t - n_\theta) e^{-\frac{(t-n_\theta)}{t_{max,G,new}}}}{t_{max,G,new}^2} \quad (24)$$

where t_{sw} is the time at which $t > n_\theta$ and $P_{eff} > P_{min}$.

$$u_G = \begin{cases} \frac{(D_G A_G - Gap)(t - n_\theta) e^{-\frac{(t-n_\theta)}{t_{max,G}}}}{t_{max,G}^2} & t > n_\theta \text{ and } P_{eff} > P_{min} \\ 0 & 0 \leq t \leq n_\theta \\ \frac{D_G A_G t e^{-\frac{t}{t_{max,G}}}}{t_{max,G}^2} & P_{eff} \leq P_{min} \end{cases} \quad (25)$$

where p_θ is a transport delay of pramlintide between its administration and its effective site resulting in an effective concentration, $P_{eff} \cdot n_\theta$ is a delay on the current meal that occurs in the presence of pramlintide, $t_{max,G,old}$ is the peak meal absorption time at the previous time point, $t_{max,G,new}$ is the peak meal absorption time at the current time point, k_{lag} is the lag constant that acts on $t_{max,G,old}$ in the presence of pramlintide, D_G is the amount of glucose given as a meal, A_G is the bioavailability, and P_{min} is the minimum pramlintide concentration.

Model Constants and Parameters

Model quantities were divided into model constants from the literature (Table 1) and model fitted parameters from this study (Table 2).

Methods

Introduction

All modeling, parameter estimations, and simulations were performed using MATLAB® 2012a (Mathworks, Inc, Natwick, MA). Original data from studies were not available. Therefore, the program GraphClick© (Arizona Software, Zurich, Switzerland, <http://www.arizona-software.ch/graphclick>) was used to get data points of mean values presented in published graphs.

Data Sets

Six previously published articles^{7,13,17,21-23} with 27 data sets were used for the modeling of both pramlintide SC PK and PD. Colburn et al²¹ and Fang et al¹³ were used for predicting

Table 1. Glucose Model Constants Hovorka et al²⁵

#	Parameter	Value
1	Patient mass (kg)	77.7
2	F_{0I} (mmol/kg min)	0.0097
3	V_G (L/kg)	0.16
4	k_{G} (min ⁻¹)	0.066
5	A_G (unitless)	0.8
6	$t_{max,G}$ (min)	40

Insulin model constants: Hovorka et al²⁵ and Wilinska et al²⁶

7	EGP_0 (mmol/kg min)	0.0161
8	k_{SQi} (dimensionless)	0.67
9	k_{SQis} (min ⁻¹)	0.0112
10	k_{SQif} (min ⁻¹)	0.0210
11	k_{ei} (min ⁻¹)	0.138
12	$V_{max,LD}$ (mU/min)	1.93
13	$K_{M,LD}$ (mU)	62.6
14	V_1 (L/kg)	0.12
15	k_{ia1} (min ⁻¹)	0.006
16	k_{ia2} (min ⁻¹)	0.06
17	k_{ia3} (min ⁻¹)	0.03
18	S_{flT} (unitless)	$51.2e^{-4}$
19	S_{flD} (unitless)	$8.2e^{-4}$
20	S_{flE} (unitless)	$520e^{-4}$

Pramlintide model constants: Clodi et al²⁰

21	k_{ep} (min ⁻¹)	0.1069
22	k_{p21} (min ⁻¹)	0.1448
23	k_{p12} (min ⁻¹)	0.1254
24	k_{p32} (min ⁻¹)	0.0164
25	k_{p23} (min ⁻¹)	0.0234

IV PK. Kong et al²³ was used for fitting SC PK, and Kolterman et al²² was used for predicting SC PK. Weyer et al⁷ was used for fitting PD, and Thompson et al,¹⁷ Kong et al,²³ Kolterman et al,²² and Fang et al¹³ were used for predicting PD.

The first article, Colburn et al,²¹ included 6 data sets and was used to test IV PK of pramlintide. This study included 24 subjects with T1DM. The 24 subjects were divided into 3 pramlintide dose groups of 8 subjects each: group A was given 30 mcg, group B was given 100 mcg, and group C was given 300 mcg. Patients in each dose group underwent a 2-period IV bolus-versus-infusion crossover. The study design included administration of usual insulin dose 30 minutes before pramlintide administration. A standardized meal was given 30 minutes after pramlintide dosage. Bolus pramlintide was given as an IV push over 2 minutes, and the infusion was given over a period of 2 hours.

The second article, Fang et al,¹³ included 6 data sets and was used to test our model's IV pramlintide PK/PD model. This study included 25 male subjects with T1DM. This study followed the same protocol used by Colburn et al.²¹

The third article, Kong et al,²³ which included 4 data sets, was used to fit SC pramlintide PK and validate PD. This

Table 2. Pramlintide Model Fitted Parameters.

#	Parameter	Low	Mean	High
1	k_{SQp} (min ⁻¹)	0.0213	0.0215	0.044
2	n_{θ} (min)	28	34	35
3	p_{θ} (min)	7	9	16
4	k_{θ} (unitless)	0.0046	0.0101	0.0216
5	P_{min}^{lag} (pmol/L)	3	3	3

study included 11 men with T1DM. Gastric emptying was measured using low-activity radioactive markers (99mTc) were attached to the surface of the subject's skin, anteriorly and posteriorly. Thirty minutes before they were due to eat, the patients injected themselves with their usual morning insulin, and 15 min later they injected the study drug (either placebo or 30, 60, or 90 mcg pramlintide) subcutaneously. At 0 min, within 10 min, they ate a standard meal consisting of a pancake, labeled with 3MBq nonabsorbable Tc-99m-ion exchange resin, and a low fat milkshake containing 3-OMG. The meal consisted of 62.5 g of carbohydrates. Gastric emptying images were obtained for the next 8 hours. At 240 min the subjects ate a similar meal.

The fourth article, Kolterman et al,²² included 3 data sets and was used to validate SC PK/PD. This study investigated the effects of a 14-day period of amylin replacement therapy on responses to a standardized IV insulin infusion and a liquid Sustacal meal in amylin-deficient T1DM subjects. This study included 84 subjects; 22 subjects were given a placebo, 18 were given 30 mcg of pramlintide, 23 were given 100 mcg of pramlintide, and 21 were given 300 mcg of pramlintide. The pramlintide dosage was given 30 minutes before the liquid Sustacal meal of 49.5 g of carbohydrates, and the insulin infusion of 40 mU kg⁻¹ hr⁻¹ for 100 minutes was given at the same time. Blood glucose, lactate, glucagon, insulin, catecholamines, calcium, and potassium levels were measured. It should be noted that plasma glucose concentrations were not given prior to the meal resulting in the fitting of the baseline glucose concentrations at $t = -30$ min (time insulin and pramlintide were administered).

The fifth article, Weyer et al,⁷ included 5 data sets and was used to fit our model's PD. Lispro insulin and regular insulin were both used in this study. However, only lispro insulin was used as our model expresses the kinetics of only lispro insulin. This study included 21 subjects. Subjects received 1 of 5 treatments (a SC injection of placebo at -15 min or 60 mcg pramlintide) at -15, 0, +15, or +30 min relative to the standardized breakfast according to a randomized sequence, after an overnight fast. The meal and insulin dosage (6-6.3 units) were given at 0 min. It should be noted for the pramlintide dosage given at $t = -15$ min relative to the meal plasma glucose concentrations were only given from $t = 0$ min (time meal and insulin were administered), resulting in the fitting of the baseline glucose concentration for this pramlintide dosage.

The final article, Thompson et al,¹⁷ included 3 data sets and was used to validate our model's PD. This study was a double-blind, randomized, placebo-controlled, parallel-group, fixed-dose study comparing the effects on 24-hour plasma glucose profiles, PK, and drug tolerance of 3 doses of pramlintide and placebo administered 4 times a day for 14 days to patients with T1DM. Insulin was given 30 minutes prior to the meal, and pramlintide dosage of 0 mcg (placebo) (42 subjects), 10 mcg (43 subjects), 30 mcg (41 subjects), or 100 mcg (42 subjects) was given 15 minutes before the meal. The meal was a standardized Sustacal meal of 75 g of carbohydrates. It should be noted that at 9:00 PM a snack of unknown quantity was given to the subjects; as a result, this snack was not included in predictions.

Performance Metrics

Root mean square error (RMSE) was used as measures of goodness of fit. Data are reported as mean \pm standard error of the mean,

$$RMSE = \sqrt{\frac{\sum (x(:,i) - x_{ref}(:,i))^2}{(n-1)}} \quad (29)$$

where x is our model's estimate, x_{ref} is the reference value and n is the number of samples.

Modified Hovorka Glucose-Insulin Model

The original modified Hovorka²⁵⁻²⁶ with glucose and lispro insulin (rapid acting) PK/PD was tested on clinical data^{7,17,22-23} using known meal amounts. Insulin amounts were fitted for all data except Weyer et al,⁷ where insulin amount was known.

Pramlintide Pharmacokinetics

IV pramlintide kinetics²⁰ were added to the modified Hovorka^{25,26} and tested with clinical data^{13,21} shown in Figures 2 and 3. Next, the IV pramlintide kinetics²⁰ were converted to SC kinetics by adapting the SC kinetics of insulin.²⁶ The original model had 7 parameters to fit. Parameters were fit to SC PK data.²³ These parameters were fit by first linearizing the model. Then, using the system identification toolbox in MATLAB, a gray-box model was created by using the "idgrey" function. Estimating parameters was done using the "greyest" command, which estimates a linear gray-box model, using time or frequency domain from experimental data. Least squares optimization was used to obtain final parameter estimates. Two of the 3 compartments were removed based on null parameter estimates. Resulting in 1 compartment with 1 added parameter, k_{SOP} . High and low parameter estimates were found by using least squares optimization 1 standard deviation from the mean. PK was validated using data found in Kolterman et al.²² Pramlintide

kinetics seem to change over time;²² to address this issue the volume at the pramlintide active site (V_p ; equation 21) was fit using least squares optimization.

Pramlintide Pharmacodynamics

Glucose parameters most likely to undergo changes by pramlintide were scrutinized. Three parameters were chosen to be tested: EGP , k_g and $t_{max,G}$, found in equations 1, 2, and 6. These parameters were tested using a linear PD equation and fit to PD data⁷ using least squares optimization. A time delay on the meal, a transport delay to the effective pramlintide compartment, and a minimum threshold concentration for pramlintide²³ were also tested. High and low parameter estimates were found by using least squares optimization 1 standard deviation from the mean. Validation of the model was done using other experimental data.^{17,22-23} Last, a study containing IV pramlintide administration¹³ was used as a prediction for PD.

Modification of the peak meal absorption time ($t_{max,G}$) equation 23 in this model affects not only dynamics but the magnitude of the meal uptake, which shows the process sensitivity of the second order pulse response used as the meal disturbance found in Hovorka et al,²⁵ equation 6. For this system, it is critical that the total meal does not change. If you modify the peak meal absorption time ($t_{max,G}$) without making a correction, you will get a different final meal amount than what was initially given. This can be seen in Figure 4a, where a step change in the time constant occurs at $t = 20$ min. Here different final meal amounts occur for different time constants ($t_{max,G}$). In Figure 4b you can see the different meal consumption at the peak meal absorption time change ($t_{max,G}$); this is the gap that needs to be compensated for mathematically to get a total meal consumed that is equal to the amount that is initially stated. In Figure 4c the same step response that was done in 4a shows the mathematical correction for the gap where final meal consumption is equal to the initial meal given with varying peak meal absorption times ($t_{max,G}$).

Results

Modified Hovorka Glucose-Insulin Model

Fitting the various placebos found in the data tested the modified Hovorka model²⁵⁻²⁶ (Tables 3 and 4; Figures 5 to 9). Fitted RMSE values range from 4.64 to 25.74 mg/dL.

Intravenous Pramlintide Pharmacokinetics

A study containing IV pramlintide PK²⁰ proposed a 3-compartment model to represent pramlintide kinetics. This model was added to the modified Hovorka glucose-insulin physiological model²⁵⁻²⁶ and compared to experimental data. Two independent studies^{13,21} contain experimental data for both a bolus and infusion (IV) of 30, 100, and 300 mcg doses of

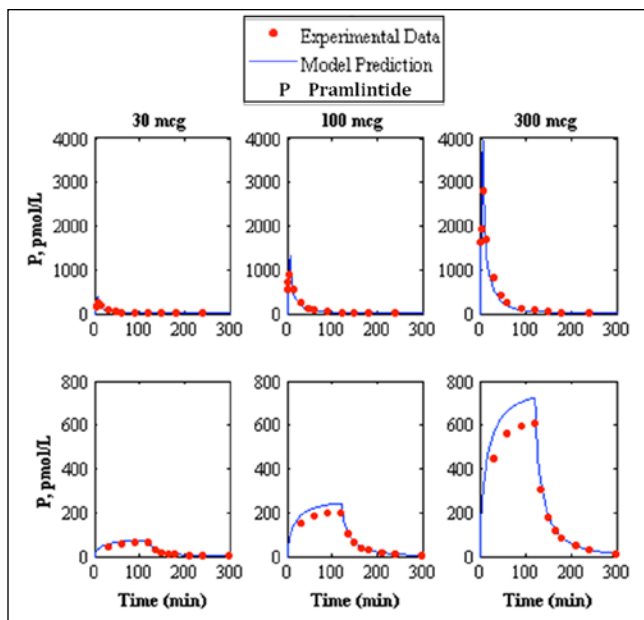


Figure 2. Comparison of intravenous pramlintide kinetics²⁰ 3-compartment model to experimental data.¹³ The top represents intravenous bolus and the bottom represents intravenous infusion, where the left, middle, and right represent pramlintide dosages of 30, 100, and 300 mcg, respectively, where the model prediction is represented by the solid line and experimental data points are represented by the dotted line.

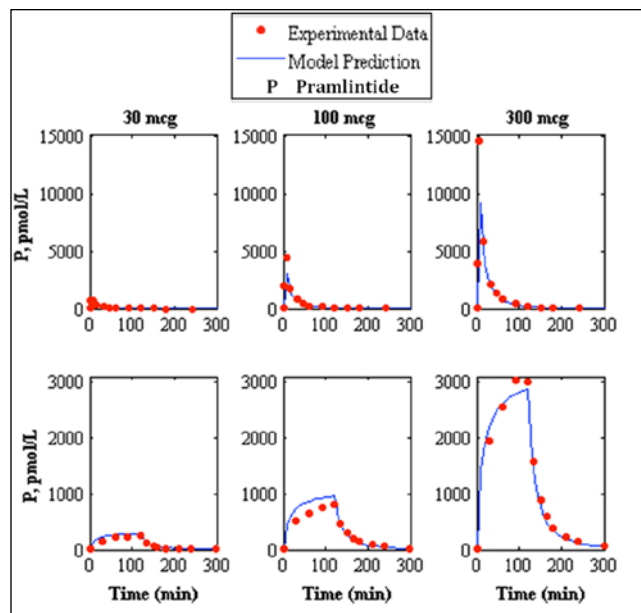


Figure 3. Comparison of intravenous pramlintide kinetics²⁰ 3-compartment model to experimental data.²¹ The top represents intravenous bolus and the bottom represents intravenous infusion where the left, middle, and right represent pramlintide dosages of 30, 100, and 300 mcg respectively, where the model prediction is represented by the solid line and experimental data points are represented by the dotted line.

pramlintide that were compared to the IV pramlintide PK model²⁰ (Figures 2 and 3 and Table 5). The goodness of fit for IV pramlintide PK has RMSE values range from 6.44 to 604.41 pmol/L.

Subcutaneous Pramlintide Pharmacokinetics

SC pramlintide kinetics were adapted²⁶ and added to IV kinetics.²⁰ Based on null parameter fits the model was reduced from a 6-compartment model to a 4-compartment model (Figure 1). Data from Kong et al²³ were used to fit parameters (Table 2); these fits are shown in Figure 6. Fitted RMSE values range from 5.24 to 10.66 pmol/L. The fit parameters were then used as predictions²² (Figure 7). Predicted RMSE values range from 1.98 to 10.39 pmol/L.

Kolterman et al²² showed a change in kinetics after 14 days. To compensate for this change, it was hypothesized that this change occurs due to a change in volume at the active site. The value of V_p (the volume at pramlintide’s active site) was fitted²² for kinetics at day 14 (Table 6). Fitted RMSE values range from 2.99 to 11.71 pmol/L.

Pramlintide Pharmacodynamics

Pramlintide PD were tested using a linear PD equation on 3 parameters: EGP , k_g , and $t_{max,G}$. EGP and k_g did not

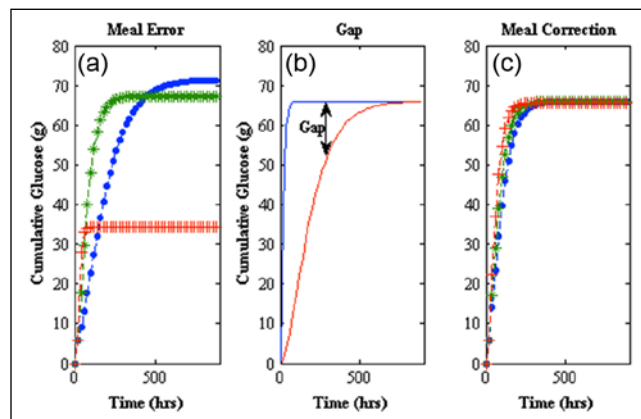


Figure 4. (a) Meal error (left) shows cumulative glucose consumed after a step change at $t = 20$ min of $t_{max,G}$ from 40 to 30 min (line with pluses), $t_{max,G}$ remaining at 40 min (line with asterisks), and $t_{max,G}$ from 40 to 50 min (line with dots). (b) A gap is created when a change in $t_{max,G}$ occurs (middle). (c) Meal correction (right) compensates for the gap created by a change in $t_{max,G}$ by using difference of the total meal consumed at previous time point and total meal consumed at current time point.

produce desired results (results not shown). A change in $t_{max,G}$ based on effective pramlintide concentration, P_{eff} and a lag constant, k_{lag} along with a lag on the meal disturbance, η_0

Table 3. Pramlintide Placebo and Subcutaneous Pharmacokinetics (PK) and Pharmacodynamics (PD), Fits Showing RMSE Values.

Reference		Placebo	PK	PD
Kong et al ²³	Conc. (mcg)	RMSE (mg/dL)	RMSE (pmol/L)	RMSE (mg/dL)
	30	19.32 ± 1.71	7.58 ± 1.75	29.99 ± 2.29
	60		5.24 ± 1.53	23.9 ± 1.89
	90		10.66 ± 3.34	26.22 ± 2.23
Weyer et al ⁷	Pramlintide time (min)			
	-15	4.64 ± 0.97	NA	28.31 ± 5.92
	0			10.63 ± 2.20
	15			12.49 ± 2.82
	30			10.48 ± 2.09

Kong et al²³ is PK fit with PD prediction, and Weyer et al⁷ is PD fit.

Table 4. Pramlintide Placebo and Subcutaneous Pharmacokinetics (PK) and Pharmacodynamics (PD) Predictions Showing RMSE Values.

Reference	Conc. (mcg)	Placebo	PK	PD
		RMSE (mg/dL)	RMSE (pmol/L)	RMSE (mg/dL)
Kolterman et al ²²	30	20.66 ± 4.89	2.99 ± 0.57	23.01 ± 5.96
	100	17.55 ± 4.89	9.79 ± 3.64	17.13 ± 4.73
	300	25.74 ± 6.17	11.71 ± 2.01	18.29 ± 5.15
Fang et al ¹³	30	NA	25.58 ± 5.69	17.02 ± 3.19
	100		274.53 ± 72.42	31.66 ± 5.08
	300		604.41 ± 149.23	42.76 ± 8.07
Thompson et al ¹⁷	10	16.4 ± 2.71	NA	34.29 ± 5.15
	30	11.17 ± 1.72		36.23 ± 5.23
	100	11.07 ± 1.76		33.86 ± 5.8

and the inclusion of a transport delay on pramlintide, p_0 afforded a desired PD effect. These parameters were fitted⁷ and shown in Table 2. Goodness of fit is shown in Table 3 and Figure 5. Fitted RMSE values range from 10.48 to 28.31 mg/dL. Fitted parameters were then used as predictions for Kong et al,²³ a study done with 2 meals, the first with pramlintide and the second without (Table 3 and Figure 6), Kolterman et al,²² a study done after 14 days of continuous pramlintide use (Table 4 and Figure 7), Thompson et al,¹⁷ a study done over 24 hours using pramlintide in 3 meals (Table 4 and Figure 8), and Fang et al,¹³ a study using IV pramlintide (Table 4 and Figure 9). The error bars shown in graphs are not the standard deviations but the variation of the individual patient data. Standard deviations were not given, and error bars in the original article were generated using an in silico patient population. Predicted RMSE values range from 17.02 to 42.76 mg/dL.

Fang et al,¹³ which has its own PK/PD model for IV pramlintide, was used as a comparator for our predictions (Table 7). Our predicted RMSE values for Fang et al¹³ ranged from 17.02 to 42.76 mg/dL. Fang et al's predicted RMSE values range from 24.97 to 62.77.

Discussion

A new in silico model of the glucose-insulin-pramlintide regulatory system has been presented. The modified Hovorka glucose-insulin physiological model²⁵⁻²⁶ was rigorously tested using placebo data. This model performed remarkably; this is especially evident with Weyer et al,⁷ where insulin dosages are kept as constant as possible. Inserting this information into the glucose-insulin model yielded excellent results with an RMSE value of 4.64 ± 0.97.

The first addition to the modified Hovorka model was an IV pramlintide PK found in a previous study²⁰ which was tested using 2 clinical studies;^{13,21} results are shown in Table 5 and Figures 2 and 3. Fang et al¹³ and Colburn et al²¹ use the same dosages of pramlintide but for varying lengths of time. Fang et al¹³ used a longer infusion and bolus (2 minute push) than used in Colburn et al²¹; plasma concentrations of pramlintide vary significantly between studies as seen in Figures 2 and 3. Interestingly, both of these studies included IV infusions of pramlintide, which yielded superior results when compared to their bolus counterparts. IV infusions have RMSE values that range from 6.44 to 68.03 pmol/L, whereas,

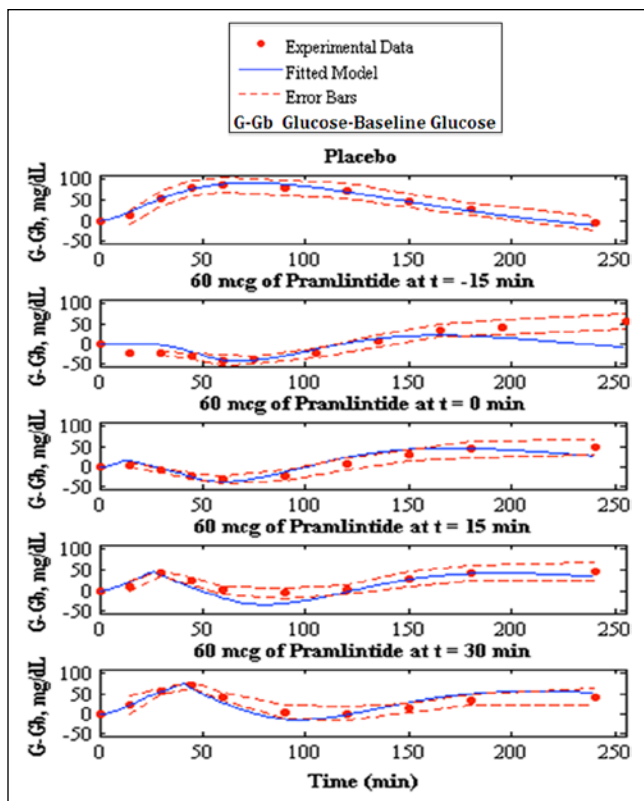


Figure 5. Fitting of pramlintide pharmacodynamics to experimental data,⁷ the top shows the placebo fit followed by pramlintide doses of 60 mcg given and $t = -15$, $t = 0$, $t = 15$ and $t = 30$ min. Model fit is represented by the solid line, experimental data points are represented by the dotted line, and the standard deviation of the experimental data is represented by the dashed line.

IV boluses have RMSE values that range from 25.58 to 604.41 pmol/L.

SC pramlintide PK required only 1 SC compartment, degradation kinetics in the SC space for pramlintide were not necessary (equations 17-22 and Figure 1). An explanation for this is that pramlintide is approximately 32% smaller than insulin, and enters through the SC layer more rapidly. Parameters were fitted using data sets from Kong et al.²³ A step response of both the IV and SC pramlintide PK indicated a time lag of approximately 55 minutes in the SC system. Results are shown in Tables 3 and 4 and Figures 6 and 7.

Kolterman et al²² showed variability in PK of pramlintide after 14 days of use and suggested that the bioavailability varied from dose to dose and acted independently over time. Investigation showed that by changing the volume at pramlintide’s active site (V_p) predictions improved considerably. One possible explanation to this is that the volume at the active site is changing over time based on multiple parameters such as cardiac output, fluid loading, and cell permeability. Results are shown in Table 6. Altered kinetics are used in Kolterman et al²² and directly affect PD (Figure 7 and Table 4).

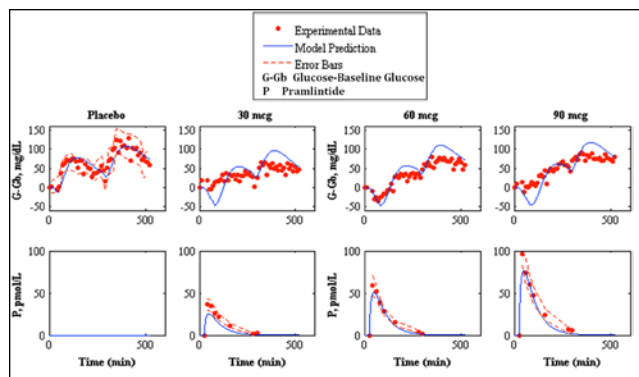


Figure 6. Fitting of pramlintide subcutaneous pharmacokinetics and prediction of pramlintide pharmacodynamics to experimental data.²³ The top shows pharmacodynamics predictions and the bottom shows pharmacokinetic fits. The left graph shows placebo fits followed by 30, 60, and 90 mcg pramlintide doses. Our model fit/prediction is represented by the solid line, experimental data points are represented by the dotted line, and the standard deviation of the experimental data is represented by the dashed line.

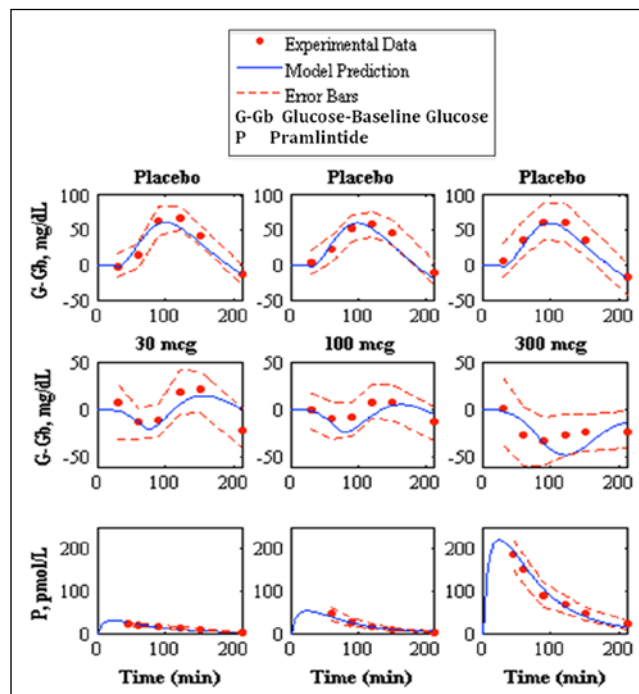


Figure 7. Prediction of pramlintide pharmacodynamics and subcutaneous pharmacokinetics to experimental data.²² The top shows the placebo fits, the middle shows pharmacodynamics predictions, and the bottom shows pharmacokinetics predictions of 30, 100, and 300 mcg pramlintide doses, left, middle, and right, respectively. Model prediction is represented by the solid line, experimental data points are represented by the dotted line, and the standard deviation of the experimental data is represented by the dashed line.

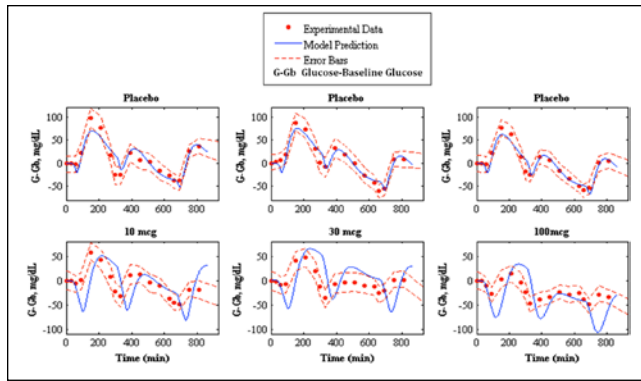


Figure 8. Prediction of pramlintide pharmacodynamics to experimental data.¹⁷ The top shows the placebo fits and the bottom shows pharmacodynamics predictions of 10, 30, and 100 mcg pramlintide doses, left middle, and right, respectively. Model prediction is represented by the solid line, experimental data points are represented by the dotted line, and the standard deviation of the experimental data is represented by the dashed line.

Pramlintide has 3 mechanisms: (1) modulates appetite, (2) suppresses glucagon secretion, and (3) slows the rate at which nutrients are delivered from the stomach to the small intestine for absorption.^{10,11} The first mechanism was disregarded because it is related to the amount of food consumed, not to the dynamics after ingestion. The second mechanism is pramlintide's action on EGP in which glucagon secretion is suppressed causing lowered EGP. For this mechanism we chose to focus on parameters EGP and k_g (see Figure 1). Where EGP is endogenous, glucose production and k_g is the transfer rate constant from the nonaccessible to the accessible compartment. The third mechanism we focused on the parameter $t_{\max,G}$, which is the peak time of glucose absorption along with an added meal delay, n_θ .

When a linear effect of pramlintide on EGP and k_G was tested, the resulting fit wasn't adequate (results not shown). A possible reason why these parameters didn't give us desired results is because the hyperglucagonemia experienced postprandially in T1DM is not captured by this model explicitly.^{25,26}

A strict meal delay, n_θ was added when pramlintide is present in the system. It was found in 2 studies^{13,23} that a meal delay occurs in the presence of pramlintide and also proved relevant in our model. In Kong et al²³ 2 meals were given, the first with pramlintide, the second without. It was found in the study that no meal delay occurred, the same is true in our model, pramlintide must be present beyond a specific P_{\min} threshold to incur a delay on the meal (n_θ) or a change in the peak meal absorption time ($t_{\max,G}$).

The parameter, P_{\min} represents the minimum pramlintide concentration to impose an effect of plasma glucose, which was postulated by Kong et al²³ to be 10 pmol/L. However, when testing pramlintide dosage of 10 mcg presented in

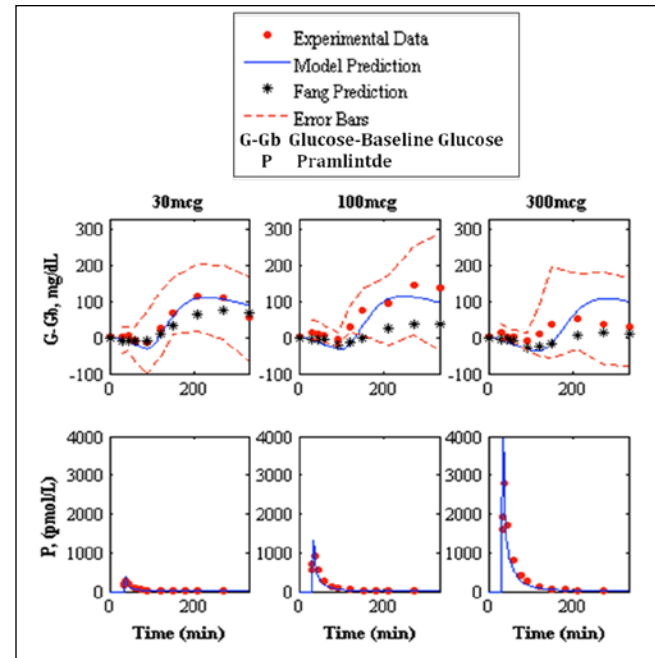


Figure 9. Prediction of pramlintide pharmacodynamics and intravenous pharmacokinetics to experimental data.¹³ The top shows the pharmacodynamics predictions and the bottom shows pharmacokinetic predictions of 30, 100, and 300 mcg pramlintide doses, left, middle, and right, respectively. Model prediction is represented by the solid line, experimental data points are represented by the dotted line, Fang et al's predicted pharmacodynamics are represented by the line with asterisks, and the standard deviation of the experimental data is represented by the dashed line.

Thompson et al¹⁷ (in which the lowest pramlintide plasma concentration is ~ 4.3 pmol/L) a pramlintide effect on plasma glucose occurs. P_{\min} was thus assumed to be a value below 10 pmol/L. However, it must be higher than the highest concentration during the second meal in Kong et al.²³ This is seen in the pramlintide dose of 100 mcg where P_{\min} must be at least 3 pmol/L to ensure no meal delay occurs for the second meal.

Slowing of gastric emptying is known to occur with pramlintide^{1,23} and was included in our model as a k_{lag} that acts on $t_{\max,G}$ linearly with respect to pramlintide concentration. A correction to the original meal disturbance equation 6 has to be done with changing $t_{\max,G}$ values as seen in equations 24 and 25. The original error can be seen in Figure 4a, the gap change is depicted in Figure 4b, and the meal correction is depicted in Figure 4c. The implemented gap correction using discretized form of equation 24 had approximately 10% inherent error using a sample time of 1 minute.

Our model also includes a pramlintide transport delay to allow the drug when administered to enter the system and reach its active site. This is demonstrated in the study Weyer et al⁷ in which pramlintide is administered at $t = -15, 0, 15,$ and 30 minutes relative to the meal. It is evident at $t = 15$ and

Table 5. Pramlintide Intravenous Pharmacokinetic Predictions Showing RMSE Values.

Reference	Pramlintide (mcg)	RMSE (pmol/L)	
Colburn et al ²¹	Bolus	30	79.42 ± 20.24
		100	148.99 ± 41.71
		300	405.62 ± 107.30
	Infusion	30	8.38 ± 1.85
		100	29.41 ± 6.51
		300	34.85 ± 7.05
Fang et al ¹³	Bolus	30	25.58 ± 5.69
		100	274.53 ± 72.42
		300	604.41 ± 149.23
	Infusion	30	6.44 ± 1.46
		100	22.77 ± 5.24
		300	68.03 ± 15.28

30 minutes that pramlintide does not incur a meal delay or slowing of gastric emptying until approximately 9 minutes after pramlintide administration.

Thompson et al¹⁷ provided the stiffest challenge to our model having 3 separate meal disturbances, insulin doses and pramlintide doses occurring in 1 in silico run. For this data set the results are mixed (see Figure 8 and Table 4). Our model appears to have a more pronounced pramlintide PD than what was experienced by the patients. Also, the underlying assumption that the patients' metabolic rate and meal uptake are identical for each meal may be incorrect. Any mismatch in the first meal will cascade to the following meals. These data seem to be at the edge of the model's capability, and it should be noted that these data were predicted, not fitted.

The final SC PKPD model had its PD parameters fitted using the 4 data sets from Weyer et al⁷ since this is the official labeling data for pramlintide used by Amylin Pharmaceuticals. All other results are predictions.^{13,17,22-23} Parameters were fitted to meet mean data values for each data set, while upper and lower extremes were fitted to obtain parameter sets for those patient types. All parameters fitted were clearly correlated and show clear trends (see Table 2) and should not be considered independent and normally distributed.

A runs test was done on Weyer et al⁷ fitted parameters to determine randomness in residuals by looking at values determined as positive and negative numbers.²⁷ Runs are a series of positives or negatives. Data found to be structured are said to have autocorrelation, which suggests that the model does not have enough information to accurately describe the system.²⁷ Pramlintide (60 mcg) at t = -15 min of the Weyer et al⁷ data set was found to have autocorrelation. A possible reason is because this particular data set did not include its first point at t = -15 min because it was not shown

Table 6. Changing Pramlintide Bioavailability Fits²² Showing V_p (Volume at Pramlintide Active Site) RMSE Values.

Pramlintide (mcg)	Original V _p		Change in V _p
	RMSE (mg/dL)	V _p (L/kg)	RMSE (mg/dL)
30	1.98 ± 0.42	0.05	2.99 ± 0.57
100	2.83 ± 0.65	0.093	9.79 ± 3.64
300	10.39 ± 3.28	0.067	11.71 ± 2.01

Table 7. Pramlintide Subcutaneous Pharmacodynamics (PD) Fits Showing RMSE Values of Our Predicted Values Versus Fang et al's¹³ Predicted Values.

Pramlintide (mcg)	PD	Fang et al PD
	RMSE (mg/dL)	RMSE (mg/dL)
30	17.02 ± 3.19	24.97 ± 5.57
100	31.66 ± 5.08	62.77 ± 13.23
300	42.76 ± 8.07	29.6 ± 5.47

in the graph found in the original article; see Figure 1b in Weyer et al,⁷ where the x label of time starts at 0. Therefore, starting point for pramlintide at t = -15 min was unknown and baseline glucose was inferred. This is also reflected in Table 3 where the RMSE values are significantly higher than the other data sets found in Weyer et al.⁷ The other data sets inclusive of t = 0 min, t = 15 min and t = 30 min showed randomness of residuals which indicates that the model includes sufficient information to capture the system. Some autocorrelation should be expected because there are effects due to glucagon that are not covered in our model. The runs test is very subjective with limited data and should not be done with less than 10 data points,²⁷ Weyer et al⁷ contains 10 data points.

The remaining 20 PKPD data sets^{13,17,22-23} were used to validate the model, and covered a wide range of experimental conditions. The dosages of pramlintide varied from 10 micrograms to 300 micrograms. Time of pramlintide dosages varied from 30 minutes before a meal to 30 minutes after a meal was consumed. SC^{7,17,22-23} and IV¹³ pramlintide boluses were evaluated. One study¹⁷ included 3 meals over 24 hours and another²³ included 2 meals over 9 hours; both of these were predicted. Meals were either Sustacal^{17,22} or standardized.^{7,13,23} The best RMSE values are 17.02 ± 3.19 and the worst RMSE values are 42.76 ± 8.07.

Fang et al¹³ previously provided the most detailed PKPD model for pramlintide except was limited to IV infusions and boluses. The objective was to compare our developed SC PKPD model, which can be used for IV and SC infusions/boluses of pramlintide to theirs.¹³ Results are in Table 7 and Figure 9 show clearly that our model does better in the 30

and 100 mcg doses, and only is poorer at the very high concentration for T1DM of 300 mcg. Both models have a fixed nondosage dependent time delay (Fang et al¹³ is 85.9 versus 34 minutes in our model, but we also have a transport delay to an effective compartment of 9 minutes). Kong et al²³ experimentally tested gastric emptying using radioactive isotopes and found time lags of 54.4, 56.4, to 70.3 minutes for doses of 30 mcg, 60 mcg, and 90 mcg given, which include both the time delay and first 10% of meal emptied, which are more in line with the model presented here. Other differences in Fang et al¹³ are the model for insulin and meal dynamics and inclusion of a sigmoidal PD effect on endogenous glucose uptake due to glucagon suppression. The latter is not present in our model. At 300 mcg, there may be a nonlinear PD effect that occurs at higher dosages as a result of receptor saturation or some other effect. In T1DM this high dosage is not standard clinical practice.

Conclusion

This nonlinear model utilizes ordinary differential equations as a means to describe the glucose-insulin-pramlintide physiological system of a T1DM patient. The model can be used to improve initial dosing as done in Micheletto et al.²⁴ but also can be used to explore other dosage regimens both in timing and quantity of the drugs. In the case of combined insulin/pramlintide therapy, the meal is extended significantly allowing more feedback to take place for additional corrective bolus(es) making glycemic regulation easier to obtain. In silico testing can readily be done to optimize possible new regimens. This compartmental model has the ability to be employed into a controller to improve current control approaches used in the artificial pancreas in which the timing and quantity of drugs can be varied based on a feedback system with the ability to adapt in real time.

Glossary

Symbol	Description
Glucose subsystem: Hovorka et al ²⁵	
States	
G_1	Masses of glucose in accessible (plasma) compartment
G_2	Masses of glucose in nonaccessible compartment
Input	
u_G	Meal disturbance
Parameters	
Patient mass	
F_{01}^c	Non-insulin-dependent glucose flux
V_G	Volume of the glucose compartment
k_g	The transfer rate constant from the nonaccessible to the accessible compartment
F_R	Renal glucose clearance
EGP	Endogenous glucose production (EGP) extrapolated to the zero insulin concentration
D_G	Amount of glucose given during meal
A_G	Availability of glucose
$t_{max,G}$	Time for peak glucose absorption
Insulin kinetic subsystem: Wilinska et al ²⁶	
States	
SQ_{is1}	Slow subcutaneous compartment 1
SQ_{if}	Fast subcutaneous compartment
SQ_{is2}	Slow subcutaneous compartment 2
$Plasma_I$	Masses of insulin in accessible (plasma) compartment
Input	
$u_{Insulin}$	Insulin dosage
Parameters	
kSQ_i	Proportion of the total input flux passing through the slower, 2 compartment channel
kSQ_{is}	Rate constant of the slow subcutaneous compartment of insulin
kSQ_{if}	Rate constant of the fast subcutaneous compartment of insulin
k_{ei}	Insulin elimination from plasma

(continued)

Symbol	Description
V_I	Insulin distribution volume
$V_{max,LD}$	Saturation level describing Michaelis Menten dynamics of insulin degradation for continuous infusion and bolus
$k_{M,LD}$	The value of insulin mass (mU) at which insulin degradation is equal to half of its maximal value for continuous infusion and bolus
Insulin dynamic subsystem: Hovorka et al ²⁵	
States	
I_1	The (remote) effects of insulin on glucose distribution/transport
I_2	The (remote) effects of insulin on glucose disposal
I_3	The (remote) effects of insulin on EGP
Parameters	
k_{ia1}	Deactivation rate—insulin action subsystem (glucose distribution/transport)
k_{ia2}	Deactivation rate—insulin action subsystem (glucose disposal)
k_{ia3}	Deactivation rate—insulin action subsystem (EGP)
S_{IT}	Insulin sensitivity of distribution/transport
S_{ID}	Insulin sensitivity of disposal
S_{IE}	Insulin sensitivity of EGP
Pramlintide kinetics subsystem: Clodi et al ²⁰	
States	
SQ_p	Pramlintide subcutaneous compartment
$Plasma_p$	Masses of pramlintide in accessible (plasma) compartment
P_2	Masses of pramlintide in nonaccessible compartment
P_3	Masses of pramlintide in nonaccessible compartment
P_{eff}	Represents effective pramlintide compartment responsible for pharmacodynamics effects on glucose
Input	
u_{Pram}	Pramlintide dosage
Parameters	
kSQ_p	Rate constant
k_{ep}	Pramlintide elimination from the plasma
V_p	Initial distribution volume
k_{p21}	Rate constant flux from compartment 2 to 1
k_{p12}	Rate constant flux from compartment 1 to 2
k_{p32}	Rate constant flux from compartment 3 to 2
k_{p23}	Rate constant flux from compartment 2 to 3
p_0	Transport delay of pramlintide from the plasma to the effective compartment
Pramlintide dynamic subsystem	
States	
$t_{max,G,old}$	Time of peak meal absorption at last time point
$t_{max,G,new}$	Time of peak meal absorption at current time point
Gap	Gap created when a change in $t_{max,G}$ occurs
Parameters	
k_{lag}	Lag constant on $t_{max,G}$
n_0	Time delay on the meal caused by pramlintide
P_{min}	Minimum effective pramlintide concentration
t_{sw}	Time at which effective pramlintide concentration changes $t_{max,G}$

Abbreviations

EGP, endogenous glucose production; IV, intravenous; MPC, model predictive control; PD, pharmacodynamics; PID, proportional integral derivative; PK, pharmacokinetics; RMSD, root mean square deviation; SC, subcutaneous; T1DM, type 1 diabetes mellitus.

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References

1. Woerle HJ, Albrecht M, Linke R, Zschau S, Neumann C. Impaired hyperglycemia-induced delay in gastric emptying in patients with type 1 diabetes deficient for islet amyloid polypeptide. *Diabetes Care*. 2008;31(12):2325-2331.
2. Bequette BW. Challenges and recent progress in the development of a closed-loop artificial pancreas. *Ann Rev Control*. 2012;36(2):255-266.
3. Steil GM, Rebrin K. Closed-loop insulin delivery—what lies between where we are and where we are going? *Expert Opin Drug Del*. 2005;2:353-362.
4. Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabetic Med*. 2006;23:1-12.
5. Renard E, Costalat G, Chevassus H, Bringer J. Artificial beta-cell: clinical experience toward an implantable closed-loop insulin delivery system. *Diabetes Metab*. 2006;32:497-502.
6. Vinik A, Nakave A. Editorial: a break in the brake mechanism in diabetes—a cause of postprandial hyperglycemia. *Diabetes Care*. 2008;31(12):2410-2412.
7. Weyer C, Gottlieb A, Kim DD, et al. Pramlintide reduces postprandial glucose excursions when added to regular insulin or insulin lispro in subjects with type 1 diabetes: a dose-timing study. *Diabetes Care*. 2003;26:3074-3079.
8. Heptulla RA, Rodriguez LM, Bomgaars L, Haymond MW. The role of amylin and glucagon in the dampening of glycemic excursions in children with type 1 diabetes. *Diabetes*. 2005;54:1100-1107.
9. Kruger DF, Gatcomb PM, Owen SK. Clinical implications of amylin and amylin deficiency. *Diabetes Educ*. 1999;25:389-397.
10. Alrefai HA, Latif KA, Hieronymus LB, Weakley CR, Moss RJ. Pramlintide: clinical strategies for success. *Diabetes Spectrum*. 2010;23(2):124-129.
11. Buse JB, Weyer C, Maggs DG. Amylin replacement with pramlintide in type 1 and type 2 diabetes: a physiological approach to overcome barriers with insulin therapy. *Clin Diabetes*. 2002;20(3):137-144.
12. Singh-Franco D, Robles G, Gazze D. Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. *Clin Ther*. 2007;29(4):535-562.
13. Fang J, Landersdorfer CB, Cirincione B, Jusko WJ. Study reanalysis using a mechanism-based pharmacokinetic/pharmacodynamic model of pramlintide in subjects with type 1 diabetes. *AAPS J*. 2012;15(1):15-29.
14. Weinzimer SA, Sherr JL, Cengiz E, et al. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with Type 1 Diabetes. *Diabetes Care*. 2012;35(10):1994-1999.
15. Palerm CC. Physiologic insulin delivery with insulin feedback: a control systems perspective. *Comput Meth Prog Bio*. 2011;102(2):130-137.
16. Rodriguez LM, Mason KJ, Haymond MW, Heptulla RA. The role of prandial pramlintide in the treatment of adolescents with type 1 diabetes. *Pediatr Res*. 2007;62(6):746-749.
17. Thompson RG, Peterson J, Gottlieb A, Mullane J. Effects of pramlintide, an analog of human amylin, on plasma glucose profiles in patients with IDDM results of a multicenter trial. *Diabetes*. 1997;46:632-636.
18. Thompson RG, Pearson L, Kolterman OG. Effects of 4 weeks' administration of pramlintide, a human amylin analogue, on glycaemia control in patients with IDDM: effects on plasma glucose profiles and serum fructosamine concentrations. *Diabetologia*. 1997;40:1278-1285.
19. Weyer C, Fineman MS, Strobel S, et al. Properties of pramlintide and insulin upon mixing. *Am J Health Syst Pharm*. 2005;62(8):816-822.
20. Clodi M, Thomaseth K, Pacini G, et al. Distribution and kinetics of amylin in humans. *Am J Physiol*. 1998;274:E903-E908.
21. Colburn WA, Gottlieb AB, Kolterman OG. Pharmacokinetics and pharmacodynamics of AC137 (25, 28, 29 tripro-amylin, human) after intravenous bolus and infusion doses in patients with insulin-dependent diabetes. *J Clin Pharmacol*. 1996;36:13-24.
22. Kolterman OG, Schwartz S, Corder C, et al. Effect of 14 days' subcutaneous administration of the human amylin analogue, pramlintide (AC137), on an intravenous insulin challenge and response to a standard liquid meal in patients with IDDM. *Diabetologia*. 1996;39:492-499.
23. Kong MF, Stubbs TA, King P, et al. The effect of single doses of pramlintide on gastric emptying of two meals in men with IDDM. *Diabetologia*. 1998;41:577-583.
24. Micheletto F, Dalla Man C, Kolterman O, et al. In silico design of optimal ratio for co-administration of pramlintide and insulin in type 1 diabetes. *Diabetes Technol*. 2013;15(10):1-8.
25. Hovorka R, Canonico V, Chassin LJ, et al. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol Meas*. 2004;25:905-920.
26. Wilinska ME, Chassin LJ, Schaller HC, Schaupp L, Pieber TR, Hovorka R. Insulin kinetics in type-1 diabetes: continuous and bolus delivery of rapid acting insulin. *IEEE Trans Biomed Eng*. 2005;52(1):3-12.
27. Chatterjee S, Ali HS. *Regression Analysis by Example*. 5th ed. Hoboken, NJ: John Wiley; 2012.