Journal of Diabetes Science and Technology
Volume 2, Issue 4, July 2008

ORIGINAL ARTICLES

A Subcutaneous Insulin Pharmacokinetic Model for Computer Simulation in a Diabetes Decision Support Role: Validation and Simulation

Jason Wong, B.Eng.,[1] J. Geoffrey Chase, Ph.D.,[1] Christopher E. Hann, Ph.D.,[1] Geoffrey M. Shaw, MBChB, FJFICM,[2] Thomas F. Lotz, Dipl. Ing, Ph.D.,[1] Jessica Lin, B.Eng., Ph.D.,[1] and Aaron J. Le Compte, B.Eng.[1]

Abstract

Objective:

The goal of this study was to validate a previously derived and identified physiological subcutaneous (SC) insulin absorption model for computer simulation in a clinical diabetes decision support role using published pharmacokinetic summary measures.

Methods:

Validation was performed using maximal plasma insulin concentration (C_{max}) and time to maximal concentration (t_{max}) pharmacokinetic summary measures. Values were either reported or estimated from 37 pharmacokinetic studies over six modeled insulin types. A validation comparison was made to equivalent pharmacokinetic summary measures calculated from model generated curves fitted to respective plasma insulin concentration data. The validation result was a measure of goodness of fit. Validation for each reported study was classified into one of four cases.

Results:

Of 37 model fits, 22 were validated on both the C_{max} and the t_{max} summary measures. Another 6 model fits were partially validated on one measure only due to lack of reporting on the second measure with errors to reported or estimated ranges of <12%. Another 7 studies could not be validated on either measure because of inadequate reported clinical data. Finally, 2 separate model fits to data from the same study failed the validation with 90 and 71% error on t_{max} only, which was likely caused by protocol-based error. No model fit failed the validation on both measures.

continued →

Author Affiliations: [1]Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand, and [2]Department of Intensive Care, Christchurch Hospital, Christchurch School of Medicine and Health Science, University of Otago, Dunedin, New Zealand

Abbreviations: (C_{max}) maximal plasma insulin concentration, (IV) intravenous, (MI) monomeric insulin, (NPH) neutral protamine Hagedorn, (PK) pharmacokinetic, (RI) regular insulin, (SC) subcutaneous, (t_{max}) time to maximal concentration

Keywords: blood glucose, compartmental models, decision support, diabetes, hyperglycemia, insulin, simulation, subcutaneous injection

Corresponding Author: Jason Wong, Department of Mechanical Engineering, University of Canterbury, Private Bag 4800, Christchurch, New Zealand; email address *xww10@student.canterbury.ac.nz*

Abstract cont.

Conclusions:

A previously derived and identified model was clinically validated for six insulin types using C_{max} and t_{max} summary measures from published pharmacokinetic studies. Hence, this article presents a clinically valid model that accounts for multiple nonlinear effects and six different types of SC insulin in a computationally modest form suitable for use in clinical decision support.

J Diabetes Sci Technol 2008;2(4):672-680

Introduction

This study reports the validation of an identified physiological compartment model of plasma insulin appearance from subcutaneous (SC) injection that is presented in this journal. A range of clinically current insulin types were modeled, specifically the prandial insulins monomeric insulin (MI) and regular insulin (RI) and the intermediate- and long-acting basal insulins neutral protamine Hagedorn (NPH) and glargine. The older insulin types lente and ultralente were also modeled. This facility enabled retrospective data of patients treated with these insulin types to be used for model identification and validation. The model was identified previously with good precision in all identified parameters using a wide range of clinical data, and this validation study aims to gauge the accuracy of this model identification using published pharmacokinetic summary measures.

If the intended role of the model is *in silico* simulation, a Monte Carlo analysis will be used to simulate physiological variability in the pharmacokinetic (PK) profile by transforming published variability (in coefficient of variation) in the key PK summary measures from clinical studies into model parameter probability distributions about the mean parameters identified from mean data. This approach differs from the normal approach of identifying the model on a small cohort of individual patient data, as the amount of information considered is considerably higher and the potential for more accurate simulation is greater.

Model Validation

Data used for model identification and now validation were collected via a literature review of relevant insulin PK studies searched in the MEDLINE and Science Citation Index Expanded (SCI-EXPANDED) databases. Only studies using direct measurement methods were considered.[1] These studies differ widely in cohort studied, methods, and protocol. However, the data is sufficient for this study where the goal is to develop a mean PK simulation model for a diabetes decision support system. A parameter fit and validation across a broad range of studies are likelier to result in an averaged PK response suitable for clinical use over a wide population. However, there are potentially three factors that may affect the accuracy of data:

1. Insulin antibodies [insulin-dependent diabetes mellitus (IDDM) cohort only]
2. Endogenous insulin production (noninsulin-dependent diabetes mellitus and normal cohorts only)
3. Insufficient cross-reactivity of test insulin with insulin assay (insulin analogue and animal insulin studies only)

Because of an almost universal lack of availability of spread data for each time point in the majority of these studies, a simpler validation criterion is proposed. Referring to **Figure 1**, two common PK summary measures, time to maximal plasma insulin concentration (t_{max}) and maximal plasma insulin concentration (C_{max}), for each fitted model curve ($t_{max,model}$ and $C_{max,model}$) can be compared to reported clinical values for each data set ($t_{max,data}$ and $C_{max,data}$). For these measures, a reported spread over the study for these two parameters ($SD_{t_{max,data}}$ and $SD_{C_{max,data}}$) is used to validate the equivalent identified model and results. Other well-accepted measures, including t_{50} (half-time to and decrease from peak) and area under curve, are not always reported uniformly by all studies and were thus not used here.

While this validation criterion may not be fully rigorous, it is the only method to assess the model fit to data in the absence of other complete data over several studies. Summary measures such as these are also used very commonly for describing insulin PKs and were thus readily available for most studies, allowing validation criteria comparison across studies. Finally, t_{max} and C_{max} describe the basic and fundamental clinical features of insulin action.

The result of this comparison is shown in **Tables 1–6**, and a summary is shown in **Table 7**. Where t_{max} or C_{max} values are not reported in the study, they are calculated from the mean PK curves used for the parameter identification. All reported measures are unit standardized and expressed as mean ± SD if reported differently. Some values are baseline corrected to match data used for parameter identification. If a summary measure is not reported and bounds cannot be estimated from reported data or if only a mean value was reported with no variation or spread, then the model fit cannot be validated on that particular measure for that particular study.

Possible validation outcomes are therefore limited to the following cases for each study:

a. The model fit is *fully validated* if both model curve t_{max} and C_{max} ($t_{max,model}$ or $C_{max,model}$) are within $SD_{t_{max}}$ and $SD_{C_{max}}$

b. The model fit is considered *partially validated* if only $C_{max,model}$ lies outside ± $SD_{C_{max,data}}$

c. If $t_{max,model}$ lies outside $t_{max,data}$ ± $SD_{t_{max,data}}$, the model fit is *invalidated* regardless of $C_{max,model}$. This case choice slightly emphasizes the qualitative shape of the model curve rather than the quantitative plasma insulin concentration.

d. Clearly, the model fit is also *invalidated* if *both* model curve t_{max} and C_{max} ($t_{max,model}$ or $C_{max,model}$) are outside $t_{max,data}$ ± $SD_{t_{max,data}}$ and $C_{max,data}$ ± $SD_{C_{max,data}}$

e. If $C_{max,model}$ cannot be validated but $t_{max,model}$ lies within $t_{max,data}$ ± $SD_{t_{max,data}}$ or vice versa, the model fit is *partially validated*

f. If both $t_{max,model}$ and $C_{max,model}$ cannot be validated, the model fit *cannot be validated* overall

In case of outcomes e and f, a percentage error is still calculated and shown in **Table 7** to provide an estimate of reliability.

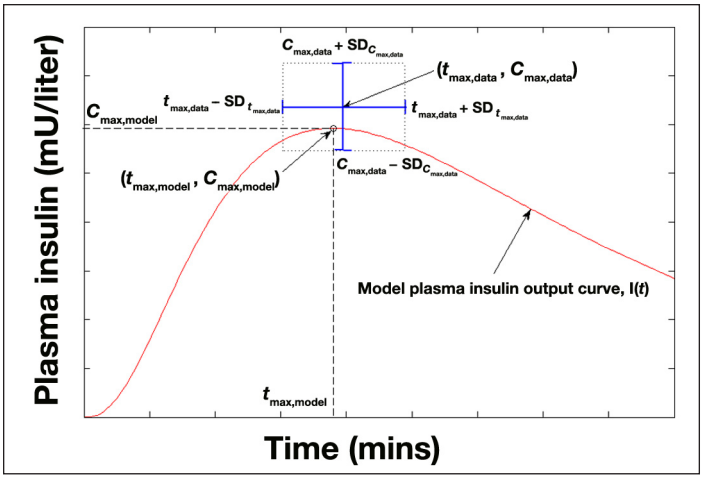

Figure 1. Schematic diagram of a plasma insulin model output curve with $t_{max,model}$ and $C_{max,model}$, and corresponding data set reported $t_{max,data}$ and $C_{max,data}$ (with standard deviation $SD_{t_{max}}$ and $SD_{C_{max}}$, respectively).

Monomeric Insulin Submodel Validation Summary

Referring to **Tables 1 and 7**, all MI model curve t_{max} and C_{max} values are fully validated (outcome a) except for the study by Shimoda and colleagues,[2] which cannot be validated (outcome f).

Table 1.
Summary Measures for Fitted MI Model Curve Compared to Published Values[a]

Parameter		Reference			
		10	2	13	14
t_{max} (min)	Modeled	47	41	52	36
	Literature	46.7 ± 23.0	31.8	49.0 ± 11.2	33.3 ± 11.6
C_{max} (mU/liter)	Modeled	26.8	32.3	39.0	22.0
	Literature	24.3 ± 14.5[b]	35.0	42.5 ± 14.5	24.6 ± 5.8

[a] Units are standardized from original reported units in literature, and values are transformed into mean ± SD if reported differently. Some values have been baseline corrected where necessary.
[b] Baseline corrected to match plotted data used for model parameter fit.

Regular Insulin Submodel Validation Summary

With reference to **Tables 2 and 7** for RI data, the study by Davis and associates[3] is invalidated (outcome c) with a very short t_{max} of 30.0 ± 7.9 minutes (for RI), resulting in 90 ± 26% error. This study underestimates t_{max} as it is not corrected for endogenous production, leading to overestimation of plasma insulin appearance in the early part of the trial where insulin production has not been fully suppressed. The 6U RI dose is also insufficient to

Table 2.
Summary Measures for Fitted RI Model Curve Compared to Published Values[a]

Parameter		Reference											
		15	16	17		2	4	18	19		3	5	
				3.3 U/ml	40 U/ml				40 U/ml	100 U/ml		NPH study	Lente study
t_{max} (min)	Modeled	65	80	53	66	107	93	84	83	112	57	83	86
	Literature	50–80[b]	83.3 ± 42.2	45–75[b]	45–90[b]	84.0	111.0 ± 58.8	92.0 ± 55.0	78.0 ± 24.0	144.0 ± 60.0	30.0 ± 7.9	108.0 ± 66.0	156.0 ± 198.0
C_{max} (mU/liter)	Modeled	59.2	43.9	73.2	63.0	10.5	37.0	20.8	39.1	30.6	26.1	87.1	75.7
	Literature	50–65[b]	51.4 ± 13.4[c]	65–90[b]	54–82[b]	8.8	27.4–33.1[b]	22.2 ± 6.0	38.1 ± 14.6	31.6 ± 12.0	24.5[b]	70.5 ± 21.7	72.8 ± 15.6

[a] Units are standardized from original reported units in literature, and values are transformed into mean ± SD if reported differently. Some values have been baseline corrected where necessary.
[b] Estimated from plotted data as value is not quoted in study.
[c] Baseline corrected to match plotted data used for model parameter fit.

fully suppress insulin production, which is confirmed by the reported C-peptide measurements.[3] Another study[4] is partially validated (outcome b) with 11.8% C_{max} error considering that insulin antibodies were unaccounted for in the IDDM cohort. Finally, as for MI, the RI model fit to the study by Shimoda and colleagues[2] cannot be validated due to a lack of fully reported data (outcome f).

Neutral Protamine Hagedorn Submodel Validation Summary

For NPH data in **Tables 3 and 7**, poor model curve t_{max} values were also obtained for Davis *et al.*[3] and Galloway *et al.*[5] compared to reported values, as shown in **Table 3**. While the model fit to the study by Davis *et al.*[3] is invalidated (outcome c), the study by Galloway and colleagues[5] is still fully validated because of the use of inadequate normal descriptive statistics for nonnormal data distribution. Similar to the RI study by Davis *et al.*,[3] these two study protocols are both uncorrected for endogenous insulin production and prescribe a relatively low dose (14 units and 0.25 U/kg, respectively) compared to other studies uncorrected for insulin production (0.4 U/kg[6,7]). Studies by Bottermann *et al.*[6] and Heinemann *et al.*[7] used higher comparative insulin doses, and Bottermann and colleagues[6] reported a negligible serum C-peptide concentration for most of the study duration.

Lente and Ultralente Submodel Validation Summary

All lente model fits are fully validated (see **Tables 4 and 7**) as are all but two ultralente model fits (see **Tables 5 and 7**), where studies by Lepore *et al.*[8] and Owens *et al.*[9] are partially validated (outcome e) with 20.5 and 8.2% C_{max} error, respectively.

Table 3.
Summary Measures for Fitted NPH Model Curve Compared to Published Values[a]

Parameter		Reference									
		20	8	21		19		6	3	5	7
				Clamp 1	Clamp 2	40 U/ml	100 U/ml				
t_{max} (min)	Modeled	260	211	228	250	197	133	211	69	82	282
	Literature	180–300[b]	240	234 ± 84	282 ± 180	288 ± 174	318 ± 276	240[b]	240 ± 56	276 ± 192	396 ± 264[c]
C_{max} (mU/liter)	Modeled	7.8	21.9	19.9	16.1	11.5	9.1	52.4	12.0	7.2	13.6
	Literature	7.5[b]	22.8 ± 9.8	23.2 ± 5.0	18.4 ± 2.3	16.2 ± 7.8	13.2 ± 4.4	63.2[b]	12.0[b]	21.8 ± 38.8	20.3 ± 5.0[c]

[a] Units are standardized from original reported units in literature, and values are transformed into mean ± SD if reported differently. Some values have been baseline corrected where necessary.
[b] Estimated from plotted data as value is not quoted in study.
[c] Summary measures quoted by study not identical to plotted values due to differences in calculation method.

Insulin Glargine Submodel Validation Summary

For insulin glargine (see **Tables 6 and 7**), Heinemann and associates[7] reported measures calculated using a different method to plotted data and cannot be validated. Using the isoglycemic clamp method, another study[8] corrected the plasma insulin concentration for insulin glargine (measured via nonspecific insulin assay) only from 3 hours onward, after the intravenous (IV) insulin infusion rate had decreased to near nil. The origin of the insulin in plasma is thus indeterminate with IV insulin infusion in this time period. Unlike the reported C_{max} (measured between 3 and 24 hours), all insulin measurements were used in the model parameter fit to data, which may have contributed to the C_{max} error of 8.5 ± 6.9% (outcome e).

In summary, it can be seen that 22 model fits are fully validated using both reported t_{max} and C_{max} summary measures, or estimated values from plotted data where not reported (see **Table 7**). A further 6 model fits are partially validated on t_{max} only (outcome b) or on C_{max} only if t_{max} cannot be validated (outcome e). All partially validated model fits have errors not exceeding 12% of reported or estimated t_{max} or C_{max} ranges. Validation cannot be performed for 7 model fits due to only a mean reported, or completely unreported, t_{max} and C_{max}, and/or if a range of t_{max} and C_{max} cannot be estimated from plotted data (outcome f). Even then, this error is <30%. Only 2 model fits failed validation with 90 ± 26 and 71 ± 23% error on t_{max} only; in both cases, significant protocol-based reasons were identified and these errors are still <100%. These data was from the same study[3] (for RI and NPH). No model fit was invalidated on both t_{max} and C_{max} measures.

As an additional validation, sample model fits to MI[10] and insulin glargine[8] data are shown in **Figures 2 and 3**. The model-generated curve using median or mean parameter values as an overall population value is shown in addition to the individual model fit curve. In both cases the results are excellent matches for data reported in these cases.

Table 4.
Summary Measures for Fitted Lente Model Curve Compared to Published Values[a]

Parameter		Reference
		5
t_{max} (min)	Modeled	200
	Literature	210 ± 174
C_{max} (mU/liter)	Modeled	25.6
	Literature	31.0 ± 15.8

[a] Units are standardized from original reported units in literature, and values are transformed into mean ± SD if reported differently. Some values have been baseline corrected where necessary.

Table 5.
Summary Measures for Fitted Ultralente Model Curve Compared to Published Values[a]

Parameter		Reference			
		21		8	9
		Clamp 1	Clamp 2		
t_{max} (min)	Modeled	495	900	477	771
	Literature	648 ± 300	816 ± 360	600	840
C_{max} (mU/liter)	Modeled	14.3	7.9	21.0	7.0
	Literature	16.4 ± 8.3	14.3 ± 8.4	25.9 ± 9.4	7.8 ± 6.0

[a] Units are standardized from original reported units in literature, and values are transformed into mean ± SD if reported differently. Some values have been baseline corrected where necessary.

Table 6.
Summary Measures for Fitted Glargine Model Curve Compared to Published Values[a]

Parameter		Reference					
		8	20		7	21	
			80 µg/ml zinc	15 µg/ml zinc		Clamp 1	Clamp 2
t_{max} (min)	Modeled	356	554	724	520	780	777
	Literature	180–1440[b]	600[c]	840[c]	822 ± 522[d]	744 ± 270	660 ± 321
C_{max} (mU/liter)	Modeled	20.5	4.1	3.8	7.0	7.9	8.0
	Literature	18.9 ± 1.3[e]	5.5[c]	4.8[c]	13.1 ± 4.3[d]	12.1 ± 5.7	10.0 ± 2.5

[a] Units are standardized from original reported units in literature, and values are transformed into mean ± SD if reported differently. Some values have been baseline corrected where necessary.
[b] Plateau time (3–24 hours).
[c] Estimated from plotted data as value is not quoted in study.
[d] Summary measures quoted by study not identical to plotted values due to differences in calculation method.
[e] Plateau concentration measured from 3 to 24 hours.

Table 7.
Summary of Model Validation to Reported t_{max} and C_{max} Summary Measures

Insulin type	Study	Within t_{max} bounds			Within C_{max} bounds			Fully validated	Partially validated	Validation cannot be performed	Validation Failed
		Yes	No	N/A	Yes	No	N/A				
MI	10	✓			✓			✓			
MI	2			✓ (29%)			✓ (8%)			✓	
MI	13	✓			✓			✓			
MI	14	✓			✓			✓			
RI	15	✓			✓			✓			
RI	16	✓			✓			✓			
RI	17	✓			✓			✓			
RI	17	✓			✓			✓			
RI	2			✓ (27%)			✓ (19%)			✓	
RI	4	✓				✓ (11.8%)			✓ [a]		
RI	18	✓			✓			✓			
RI	19	✓			✓			✓			
RI	19	✓			✓			✓			
RI	3		✓ (90 ± 26%)				✓ (7%)				✓ [a]
RI	5	✓			✓			✓			
RI	5	✓			✓			✓			
NPH	20	✓					✓ (4%)		✓ [a]		
NPH	8			✓ (12%)	✓				✓ [a]		
NPH	21	✓			✓			✓			
NPH	21	✓			✓			✓			
NPH	19	✓			✓			✓			
NPH	19	✓			✓			✓			
NPH	6			✓ (12%)			✓ (17%)			✓	
NPH	3		✓ (71 ± 23%)		✓						✓ [a]
NPH	5	✓			✓			✓			
NPH	7			✓	✓		✓			✓	
Lente	5	✓			✓			✓			
Ultralente	21	✓			✓			✓			
Ultralente	21	✓			✓			✓			
Ultralente	8			✓ (21%)	✓				✓ [a]		
Ultralente	9			✓ (8%)	✓				✓ [a]		
Glargine	8	✓				✓ (8.5 ± 6.9 %)			✓ [a]		
Glargine	20			✓ (8%)			✓ (26%)				
Glargine	20			✓ (14%)			✓ (21%)			✓	
Glargine	7			✓			✓			✓	
Glargine	21	✓			✓			✓		✓	
Glargine	21	✓			✓			✓			

[a] Refer to the text for a list of partial and failed validation outcomes.

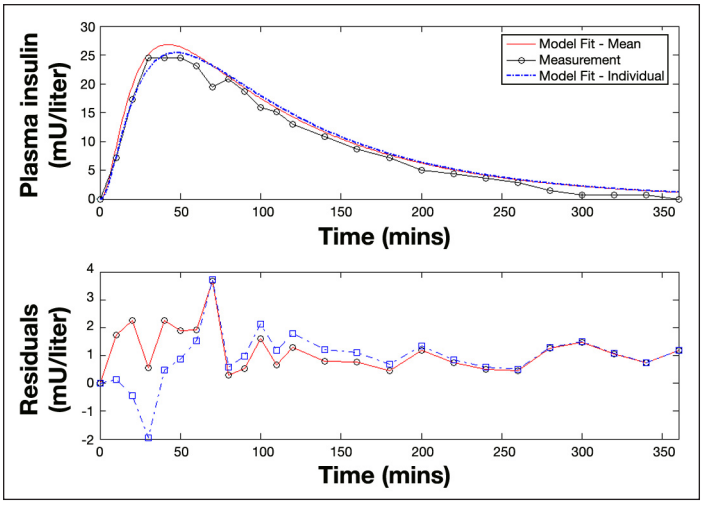

Figure 2. MI model fit to data of Plank *et al*.[10]

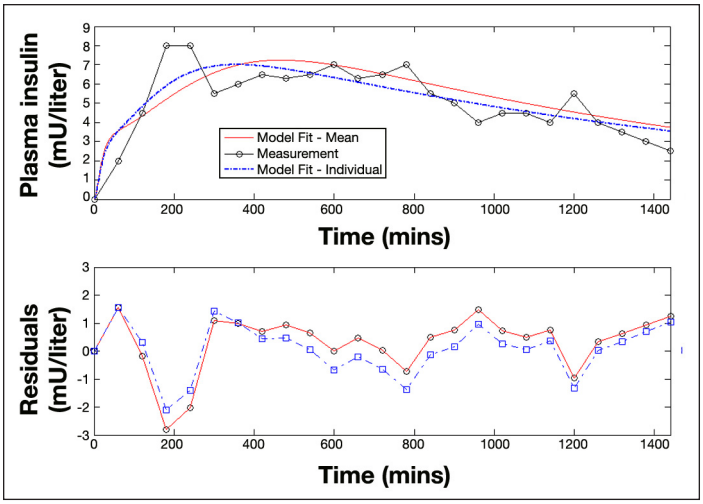

Figure 3. Insulin glargine model fit to data of Lepore *et al*.[8] Note that the plasma insulin concentration is corrected for cross-reactivity with insulin glargine only between 3 and 24 hours, i.e., the first three data points are inaccurate in respect to the exogenous insulin glargine concentration in plasma due to the presence of a not insignificant IV insulin infusion.

Model Simulation and Outputs

A comparison of model outputs using the population model parameters for an injection of 10 units for all insulin types is shown in **Figure 4**. Results are compared to output from the AIDA insulin PK model[11] by Berger and Rodbard,[12] which uses a nonlinear noncompartmental model. This model is one of the foremost SC insulin PK models developed for computer simulation of multiple insulin types and was subsequently applied in the AIDA diabetes education and decision support system. While the most complete of insulin models, it does not model MI or insulin glargine absorption, as it was first published in 1989 before these types were developed. As shown in **Figure 4**, the dynamics of each modeled insulin type are visually similar between the two models, providing an additional measure of validation.

The model dynamics are also demonstrated for RI concentration dependency and insulin glargine dose dependency in **Figure 5**. For a given RI dose, the

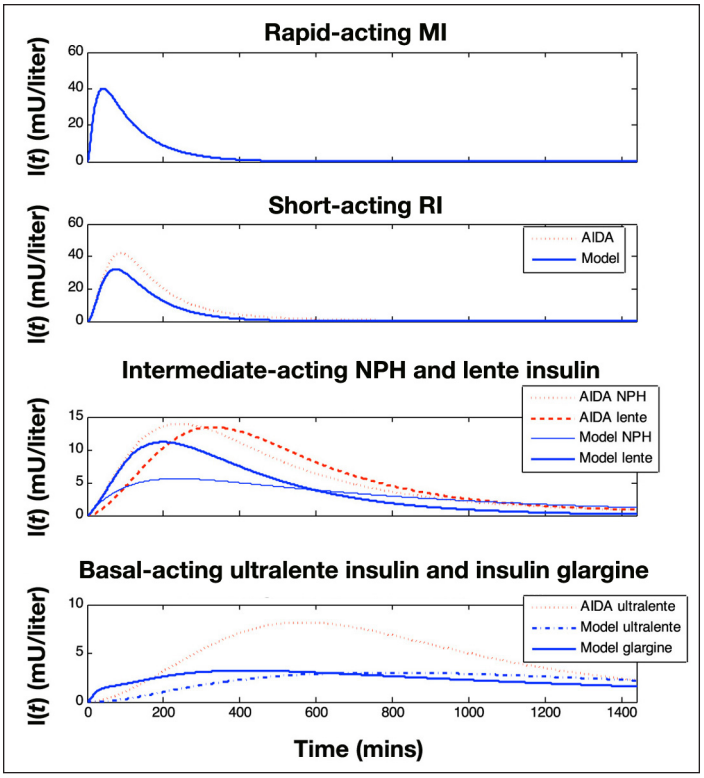

Figure 4. Comparison of model output and the AIDA insulin SC PK model for a 10-unit injection of all insulin types.[11,12] Published in 1989, the AIDA model does not model MI or insulin glargine absorption.

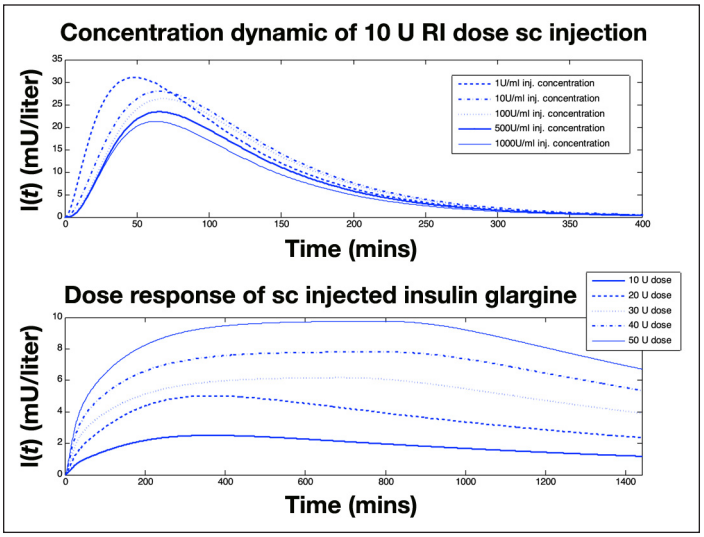

Figure 5. Dynamics of RI concentration dependency and insulin glargine dose response demonstrated by the model.

rate of absorption decreases with increasing insulin concentrations until 500 U/ml, where it begins to increase slightly. This latter phenomenon has not been reported in any study, although such high concentrations are rarely, if ever, used clinically. For a given dose, the absorption rate usually decreases with an increasing concentration of insulin preparation. However, while the mass in the hexameric state increases, the rate of diffusive loss, k_d, from the dimeric/monomeric compartment drops markedly with decreasing injection volume, which ultimately results in an increasing net rate of absorption at very high concentrations of injected insulin concentration.

Conclusions

The identified model was validated using the simple widely reported criterion of t_{max} and C_{max} PK summary measures reported the most consistently in these studies. Of 37 model fits, 22 were validated on both summary measures reported by each study or estimated from plotted data used for parameter fit where not reported. An additional 6 model fits were partially validated on t_{max} only or on C_{max} if and only if t_{max} could not be validated. All partially validated model fits had errors not exceeding 12% of reported or estimated t_{max} or C_{max} ranges. Another 7 studies could not be validated because of unreported data or reporting of only the mean values of t_{max} and C_{max} and because a range of t_{max} and C_{max} could not be estimated from data reported in the study. Finally, 2 model fits from the same study failed the validation with 90 and 71% error on t_{max} only, respectively, which is likely to be protocol based. No model fit failed the validation for both reported t_{max} and C_{max} values. Overall, the model was reasonably validated in whole or in part across 35 of 37 studies with low errors. These results show the ability of the model to capture the fundamental dynamics of insulin action for several insulin types based on data from a wide range of studies using a unified consistent PK model.

Funding:

The authors thank the Tertiary Education Commission Te Amorangi Matauranga Matua Bright Futures Top Achiever Doctoral Scholarship for financial support.

References:

1. Heinemann L, Anderson JH Jr. Measurement of insulin absorption and insulin action. Diabetes Technol Ther. 2004;6(5):698-718.
2. Shimoda S, Nishida K, Sakakida M, Konno Y, Ichinose K, Uehara M, Nowak T, Shichiri M. Closed-loop subcutaneous insulin infusion algorithm with a short-acting insulin analog for long-term clinical application of a wearable artificial endocrine pancreas. Front Med Biol Eng. 1997;8(3):197-211.
3. Davis SN, Thompson CJ, Brown MD, Home PD, Alberti KG. A comparison of the pharmacokinetics and metabolic effects of human regular and NPH insulin mixtures. Diabetes Res Clin Pract. 1991;13(1-2):107-17.
4. Kang S, Creagh FM, Peters JR, Brange J, Vølund A, Owens DR. Comparison of subcutaneous soluble human insulin and insulin analogs (Aspb9,Glub27-Aspb10-Aspb28) on meal-related plasma-glucose excursions in type I diabetic subjects. Diabetes Care. 1991;14(7):571-7.
5. Galloway JA, Spradlin CT, Nelson RL, Wentworth SM, Davidson JA, Swarner JL. Factors influencing the absorption, serum-insulin concentration, and blood-glucose responses after injections of regular insulin and various insulin mixtures. Diabetes Care. 1981;4(3):366-76.
6. Bottermann P, Gyaram H, Wahl K, Ermler R, Lebender A. Insulin concentrations and time-action profiles of three different intermediate-acting insulin preparations in nondiabetic volunteers under glucose-controlled glucose infusion technique. Diabetes Care. 1982;5 Suppl 2:43-52.
7. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care. 2000;23(5):644-9.
8. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes. 2000;49(12):2142-8.
9. Owens DR, Vora JP, Heding LG, Luzio S, Ryder RE, Atiea J, Hayes TM. Human, porcine and bovine ultralente insulin: subcutaneous administration in normal man. Diabet Med. 1986;3(4):326-9.
10. Plank J, Wutte A, Brunner G, Siebenhofer A, Semlitsch B, Sommer R, Hirschberger S, Pieber TR. A direct comparison of insulin analogs aspart and lispro in type 1 diabetic patients. Diabetes Care. 2002;25(11):2053-7.
11. Lehmann ED, Deutsch T. A physiological model of glucose-insulin interaction in type 1 diabetes mellitus. J Biomed Eng. 1992;14(3):235-42.
12. Berger M, Rodbard D. Computer simulation of plasma insulin and glucose dynamics after subcutaneous insulin injection. Diabetes Care. 1989;12(10):725-36.
13. Hedman CA, Lindström T, Arnqvist HJ. Direct comparison of insulin lispro and aspart shows small differences in plasma insulin profiles after subcutaneous injection in type 1 diabetes. Diabetes Care. 2001;24(6):1120-1.
14. von Mach MA, Brinkmann C, Hansen T, Weilemann LS, Beyer J. Differences in pharmacokinetics and pharmacodynamics of insulin lispro and aspart in healthy volunteers. Exp Clin Endocrinol Diabetes. 2002;110(8):416-9.
15. Kobayashi T, Sawano S, Itoh T, Kosaka K, Hirayama H, Kasuya Y. The pharmacokinetics of insulin after continuous subcutaneous infusion or bolus subcutaneous injection in diabetic patients. Diabetes. 1983;32(4):331-6.
16. Cernea S, Kidron M, Wohlgelernter J, Modi P, Raz I. Comparison of pharmacokinetic and pharmacodynamic properties of single-dose oral insulin spray and subcutaneous insulin injection in healthy subjects using the euglycemic clamp technique. Clin Ther. 2004;26(12):2084-91.
17. Kraegen EW, Chisholm DJ. Insulin responses to varying profiles of subcutaneous insulin infusion: kinetic modelling studies. Diabetologia. 1984;26(3):208-13.

18. Berger M, Cüppers HJ, Hegner H, Jörgens V, Berchtold P. Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. Diabetes Care. 1982;5(2):77-91.

19. Hübinger A, Weber W, Jung W, Wehmeyer K, Gries FA. The pharmacokinetics of two different concentrations of short-acting insulin, intermediate-acting insulin, and an insulin mixture following subcutaneous injection. Clin Investig. 1992;70(7):621-6.

20. Owens DR, Coates PA, Luzio SD, Tinbergen JP, Kurzhals R. Pharmacokinetics of I-125-labeled insulin glargine (HOE 901) in healthy men: comparison with NPH insulin and the influence of different subcutaneous injection sites. Diabetes Care. 2000;23(6): 813-9.

21. Scholtz HE, Pretorius SG, Wessels DH, Becker RH. Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. Diabetologia. 2005;48(10):1988-95.