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ORIGINAL ARTICLE

Pharmacokinetics of Insulin Aspart and Glucagon in Type 1 Diabetes during Closed-Loop Operation

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Abstract

Background:

We assessed the pharmacokinetics of subcutaneous insulin aspart and glucagon during closed-loop operation and their relationship with body composition variables.

Methods:

We retrospectively analyzed data collected from closed-loop experiments in 15 type 1 diabetes patients (age 47.1 ± 12.3 years, body mass index 25.9 ± 4.6 kg/m^2, glycated hemoglobin 7.9% ± 0.7%). Patients received an evening meal accompanied with prandial insulin bolus and stayed in the clinical facility until the next morning. Glucose levels were regulated by dual-hormone closed-loop delivery. Insulin and glucagon were delivered using two subcutaneous infusion pumps installed on the abdominal wall. Plasma insulin and glucagon were measured every 10–30 min. Percentage of body fat, percentage of fat in the abdominal area, and mass of abdominal fat were measured by dual X-ray absorptiometry.

Results:

A pharmacokinetic model estimated time-to-peak plasma concentrations [t_{max} insulin 51 (19) min, t_{max} glucagon 19 (4) min, mean (standard deviation)], metabolic clearance rate [*MCR* insulin 0.019 (0.015–0.026) liter/kg/min, *MCR* glucagon 0.012 (0.010–0.014) liter/kg/min, median (interquartile range)], and the background plasma concentrations [I_b insulin 10.2 (6.3–15.2) mU/liter, I_b glucagon 50 (45–56) pg/ml, median (interquartile range)]. t_{max} correlated positively between insulin and glucagon (r = 0.7; p = .007) while *MCR* correlated negatively (r = -0.7; p = .015). In this small sample size, t_{max}, *MCR*, and I_b of insulin and glucagon did not correlate with percentage of body fat, percentage of fat in the abdominal area, or total mass of abdominal fat.

Conclusions:

Insulin and glucagon pharmacokinetics might be related during closed-loop operation. Our data suggest that slower absorption of insulin is associated with slower absorption of glucagon. Body composition does not seem to influence insulin and glucagon pharmacokinetics.

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Introduction

Advances in insulin pumps and glucose sensors have motivated the development of closed-loop delivery systems.[1] Generally, two configurations of closed-loop delivery are proposed: one that infuses insulin and another that infuses insulin and glucagon. Closed-loop systems deliver insulin and glucagon based on glucose sensor readings as guided by dosing algorithms at 1 to 15 min intervals. Closed-loop systems might improve glycemic control and reduce the risk of hypoglycemia compared with conventional pump therapy.[2,3]

Delayed insulin absorption would likely hinder the performance of closed-loop systems.[4,5] We aimed to assess the pharmacokinetics of insulin aspart and glucagon during closed-loop operation and to assess their relationship with body composition variables, as these are known to potentially affect insulin absorption and action.[6,7]

Methods

Participants and Setting

We retrospectively analyzed data collected from 15 closed-loop experiments from a randomized trial[3] assessing the performance of dual-hormone closed-loop delivery in 15 adults with type 1 diabetes (age 47.1 ± 12.3 years, body mass index 25.9 ± 4.6 kg/m^2, glycated hemoglobin 7.9% ± 0.7%). All participants provided written informed consent. The study was approved by the local ethics committee.

Study Procedures

Patients received an evening meal at 19:20 accompanied with prandial insulin bolus and stayed in the clinical facility until 07:00 the next morning. Glucose levels were regulated by glucose-responsive dual-hormone closed-loop delivery. Variable insulin aspart (NovoRapid®, Novo Nordisk, Mississauga, Canada) and miniboluses of recombinant glucagon (GlucaGen®, Paladin, Canada) were delivered in the abdominal tissue using two subcutaneous infusion pumps (MiniMed Paradigm Veo®, Medtronic, Northridge, CA) according to glucose sensor readings and a predictive dosing algorithm at 10 min intervals. Venous blood samples were drawn every 10–30 min for the determination of plasma insulin and plasma glucagon. Details of study procedures are reported elsewhere.[3]

Assays and Measurements

Plasma insulin and plasma glucagon were measured in duplicate by immunoassay (Millipore, Billerica, MA). Percentage of body fat, percentage of fat in the abdominal area, and mass of abdominal fat were measured by dual X-ray absorptiometry.

Data Analysis

Absorption of insulin/glucagon was described with the two-compartment model that was previously used by Haidar and coauthors:[7]

$$\frac{dQ_1(t)}{dt} = u(t) - \frac{Q_1(t)}{t_{max}} \qquad Q_1(0) = u(0)t_{max} + Q_1$$

$$\frac{dQ_2(t)}{dt} = \frac{Q_1(t)}{t_{max}} - \frac{Q_2(t)}{t_{max}} \qquad Q_2(0) = Q_1(0) + Q_2$$

where $Q_1(t)$ and $Q_2(t)$ (units) are insulin/glucagon masses, $u(t)$ (units per minute) is the delivery rate, and t_{max} (minutes) is time to peak plasma concentration. Q_1 and Q_2 (units) are the insulin on board due to previous insulin delivery and were set to zero when glucagon data were fitted. Data were fitted starting from the late postprandial period (16:00) when insulin concentrations were dropping. We accounted for this by adding the parameters Q_1 and Q_2.[8] The insulin/glucagon plasma concentration $C(t)$ is obtained assuming fast equilibration in the plasma space:

$$C(t) = \frac{1}{t_{max}} \frac{Q_2(t)}{w.MCR} \times 10^6 + I_b,$$

where MCR (milliliters per kilogram per minute) is the metabolic clearance rate, I_b (milliunits per liter or picograms per milliliter) is the background plasma insulin/glucagon concentration and w (kilograms) is body weight. Assuming that I_b is zero, the model indicates that the appearance and the elimination in the plasma space are proportional to those of the second compartment. The background concentration is a reflection of the endogenous production of insulin/glucagon. In the absence of exogenous administration, glucagon concentrations are nonzero in type 1 diabetes, and these concentrations are not altered during hypoglycemia or exercise.[9,10] For insulin, an ultrasensitive assay documented that C-peptide secretion persists over decades but decreases with disease duration.[11] A study in 70 type 1 diabetes subjects found that I_b estimated by the same model also decreased with diabetes duration.[7]

Individual insulin/glucagon pharmacokinetic parameters (t_{max}, MCR, and I_b) were estimated using a stochastic modeling approach with WinBUGS version 1.4[12] and WBDiff version 1.9.4 (MRC Biostatistics, Cambridge, UK). Insulin and glucagon delivery were considered as forcing functions. The measurement error associated with the insulin and glucagon were assumed to be multiplicative with a coefficient of variation of 6% and 9%, respectively. **Figures 1** and **2** show sample model fits to plasma insulin and plasma glucagon concentrations.

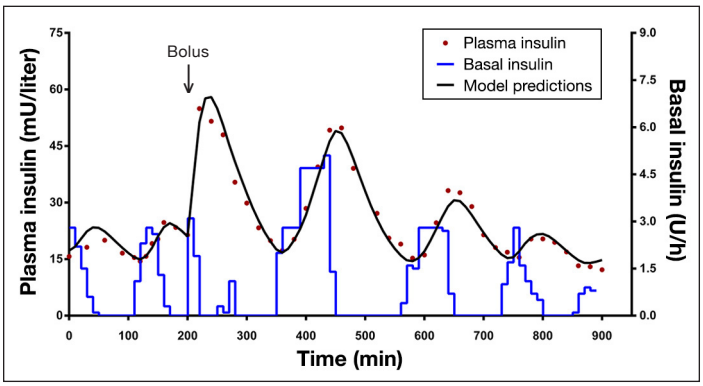

Figure 1. A sample fit of plasma insulin concentration.

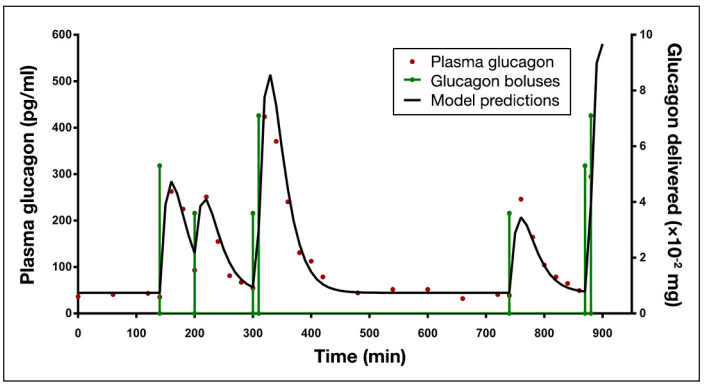

Figure 2. A sample fit of plasma glucagon concentration.

Statistical Analysis

Correlations were evaluated using the Pearson correlation coefficient. Ranked normal score transformation was used to correct for non-normality. Statistical analyses were performed using SPSS 17.0.

Results

Time to peak plasma insulin and glucagon concentrations, t_{max}, were comparable to literature data in type 1 diabetes[7,13] [insulin 51 (19) min, glucagon 19 (4) min, mean (standard deviation)]. t_{max} correlated positively between insulin and glucagon (r = 0.7; p = .007). Metabolic clearance rate of insulin was also comparable to literature data in type 1 diabetes [0.019 (0.015–0.026) liter/kg/min, median (interquartile range)] and was slightly higher than MRC for glucagon [0.012 (0.010-0.014) liter/kg/min, median (interquartile range)]. Insulin and glucagon MCR correlated negatively (r = –0.7; p = .015). **Table 1** shows the pharmacokinetics parameters of insulin and glucagon. t_{max}, MCR, and I_b of insulin and glucagon did not correlate with percentage of body fat, percentage of fat in the abdominal area, or total mass of abdominal fat (**Table 2**).

Discussion

We estimated pharmacokinetic parameters of insulin and glucagon during closed-loop operation in patients with type 1 diabetes. Insulin absorption rate correlated positively between insulin and glucagon, while MCR correlated negatively.

Table 1.
Pharmacokinetic Parameters of Insulin Aspart and Glucagon[a]

	t_{max}	*MCR*	I_b
Insulin aspart	51 (19) min	0.019 (0.015–0.026) liter/kg/min	10.2 (6.3–15.2) mU/liter
Glucagon	19 (4) min	0.012 (0.01–0.014) liter/kg/min	50 (45–56) pg/ml
Correlation between insulin and glucagon parameters	0.7[b]	-0.7[c]	0.5

[a] Data are mean (standard deviation) or median (interquartile range).
[b] p = .007.
[c] p = .015.

Pharmacokinetics did not correlate with percentage of body fat, percentage of fat in the abdominal area, or total mass of abdominal fat.

Table 2.
Correlations between Pharmacokinetics Parameters and Body Composition Variables[a]

	t_{max}	*MCR*
Insulin Parameters		
Percentage of body fat	0.13	0.19
Percentage of fat in the abdominal area	-0.07	0.35
Total mass of abdominal fat	-0.13	0.08
Glucagon Parameters		
Percentage of body fat	0.15	-0.1
Percentage of fat in the abdominal area	0.16	-0.18
Total mass of abdominal fat	0.15	0.02

[a] All $p > .05$

During closed loop, patients with slow insulin absorption have an increased risk of hypoglycemia.[4,13] Our data suggest that these patients are also likely to exhibit slower absorption of glucagon. This slow absorption might hinder the efficacy of glucagon in counteracting falling glucose levels during closed loop. However, hypoglycemia was almost absent in all our 15 patients, but this delayed glucagon absorption might have an effect in different experimental protocols such as intense prolonged exercise.

The correlation between insulin and glucagon absorption rates might be explained by the abdominal tissue composition. Literature data suggest that subcutaneous fat thickness decelerates insulin absorption[14] and is likely to affect glucagon pharmacokinetics. There is also evidence that higher body fat might influence insulin and glucagon action.[15,16] We thus investigated whether percentage of fat in the abdomen and total mass of abdominal fat correlates with either insulin or glucagon absorption rates. No significant correlation was found. However, these findings should be confirmed with a larger sample size.

We estimated mean *MCR* of insulin and glucagon similar to literature data in type 1 diabetes (*MCR* glucagon 0.012 versus 0.011 ml/kg/min, *MCR* insulin 0.019 versus 0.017 ml/kg/min; comparison against Alford and coauthors[17] and Haidar and coauthors[7]). *MCR* of insulin was higher than *MCR* of glucagon, but the two correlated negatively. Exact physiological interpretation of this negative correlation needs to be confirmed and further explored.

Knowledge of correlations between insulin and glucagon pharmacokinetics parameters might improve closed-loop algorithms. Adaptive algorithms aiming at estimating absorption rates might assume linear relationship between insulin and glucagon t_{max} mitigating nonidentifiability and allowing better estimates in real time. Algorithms based on fixed competing models[2] might also incorporate this knowledge in their fixed parameters.

Most pharmacokinetics studies used a noncompartment approach during clamp[18] or postprandial conditions,[5,19] with fewer studies adopting the compartment approach.[13,20,21] Our data included repetitive glucagon boluses that might have had an overlapping effect (e.g., **Figure 2**; t = 300 min). Our data are also limited by the lack of standardization in dosing and timing of insulin and glucagon delivery. We utilized a two-compartment model[7] to account for the repetitive glucagon boluses and the lack of delivery standardization. However, theoretically, a compartment approach will still not be able provide estimates of kinetic parameters if the data are not rich enough. For example, if basal insulin delivery is unchanged and only steady-state data exist, we will not be able to infer t_{max}, but our data included prandial bolus and overnight period of varying basal insulin (total is 47 measurements per 15 h experiment).

Also, as we did not infuse any isotope tracers, we were not able to study the effect of concurrent insulin and glucagon infusion on hepatic glucose production.

Conclusions

In conclusion, subcutaneous absorption rate correlated positively between insulin and glucagon while metabolic clearance rate correlated negatively. In our 15 subjects, insulin and glucagon pharmacokinetics did not correlate with percentage of body fat, percentage of fat in the abdominal area, or total mass of abdominal fat.

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Disclosures:

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References:

1. Hovorka R. Closed-loop insulin delivery: from bench to clinical practice. Nat Rev Endocrinol. 2011;7(7):385–95.
2. Hovorka R, Allen JM, Elleri D, Chassin LJ, Harris J, Xing D, Kollman C, Hovorka T, Larsen AM, Nodale M, De Palma A, Wilinska ME, Acerini CL, Dunger DB. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet. 2010;375(9716):743–51.
3. Haidar A, Legault L, Dallaire M, Alkhateeb A, Coriati A, Messier V, Cheng P, Millette M, Boulet B, Rabasa-Lhoret R. Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. CMAJ. 2013;185(4):297–305.
4. Nodale M, Elleri D, Allen JM, Kumareswaran K, Harris J, Haidar A, Leelarathna L, Caldwell K, Murphy HR, Wilinska ME, Acerini CL, Evans ML, Dunger DB, Hovorka R. Factors affecting performance of overnight closed-loop insulin delivery in type 1 diabetes (T1D). Diabetes. 2012;61 Suppl 1:A59.
5. Plank J, Wutte A, Brunner G, Siebenhofer A, Semlitsch B, Sommer R, Hirschberger S, Pieber TR. A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. Diabetes Care. 2002;25(11):2053–7.
6. Momesso DP, Bussade I, Lima GA, Fonseca LP, Russo LA, Kupfer R. Body composition, metabolic syndrome and insulin resistance in type 1 diabetes mellitus. Arq Bras Endocrinol Metabol. 2011;55(3):189–93.
7. Haidar A, Elleri D, Kumareswaran K, Leelarathna L, Allen JM, Caldwell K, Murphy HR, Wilinska ME, Acerini CL, Evans ML, Dunger DB, Nodale M, Hovorka R. Pharmacokinetics of insulin aspart in pump-treated subjects with type 1 diabetes: reproducibility and effect of age, weight, and duration of diabetes. Diabetes Care. 2013;36(10):e173–4.
8. Haidar A, Wilinska M, Graveston J, Hovorka R. Stochastic virtual population of subjects with type 1 diabetes for the assessment of closed loop glucose controllers. IEEE Trans Biomed Eng. 2013. Epub ahead of print.
9. Diabetes Research in Children Network (DirecNet) Study Group. Impaired overnight counterregulatory hormone responses to spontaneous hypoglycemia in children with type 1 diabetes. Pediatr Diabetes. 2007;8(4):199–205.
10. Tansey MJ, Tsalikian E, Beck RW, Mauras N, Buckingham BA, Weinzimer SA, Janz KF, Kollman C, Xing D, Ruedy KJ, Steffes MW, Borland TM, Singh RJ, Tamborlane WV; Diabetes Research in Children Network (DirecNet) Study Group. The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. Diabetes Care. 2006;29(1):20–5.
11. Wang L, Lovejoy NF, Faustman DL. Persistence of prolonged C-peptide production in type 1 diabetes as measured with an ultrasensitive C-peptide assay. Diabetes Care. 2012;35(3):465–70.
12. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. Stat Comput. 2000;10:325–37.
13. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med. 2010;2(27):27ra27.
14. Sindelka G, Heinemann L, Berger M, Frenck W, Chantelau E. Effect of insulin concentration, subcutaneous fat thickness and skin temperature on subcutaneous insulin absorption in healthy subjects. Diabetologia. 1994;37(4):377–80.

15. Bonnet F, Ducluzeau PH, Gastaldelli A, Laville M, Anderwald CH, Konrad T, Mari A, Balkau B; RISC Study Group. Liver enzymes are associated with hepatic insulin resistance, insulin secretion, and glucagon concentration in healthy men and women. Diabetes. 2011;60(6):1660–7.

16. Charbonneau A, Couturier K, Gauthier MS, Lavoie JM. Evidence of hepatic glucagon resistance associated with hepatic steatosis: reversal effect of training. Int J Sports Med. 2005;26(6):432–41.

17. Alford FP, Bloom SR, Nabarro JD. Glucagon metabolism in man, studies on the metabolic clearance rate and the plasma acute disappearance time of glucagon in normal and diabetic subjects. J Clin Endocrinol Metab. 1976;42(5):830–8.

18. Heinemann L, Weyer C, Rauhaus M, Heinrichs S, Heise T. Variability of the metabolic effect of soluble insulin and the rapid-acting insulin analog insulin aspart. Diabetes Care. 1998;21(11):1910–4.

19. 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.

20. Clausen WH, De Gaetano A, Vølund A. Within-patient variation of the pharmacokinetics of subcutaneously injected biphasic insulin aspart as assessed by compartmental modelling. Diabetologia. 2006;49(9):2030–8.

21. Potocka E, Baughman RA, Derendorf H. Population pharmacokinetic model of human insulin following different routes of administration. J Clin Pharmacol. 2011;51(7):1015–24.