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

Ahmad Haidar, Ph.D.,1,2 Claire Duval,1,3 Laurent Legault, M.D.,4 Rémi Rabasa-Lhoret, M.D., Ph.D.1,2,5

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/m², 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.


Keywords: artificial pancreas, closed-loop systems, glucagon, insulin aspart, pharmacokinetics, type 1 diabetes

Author Affiliations: 1Institut de Recherches Cliniques de Montréal, Montreal, Canada; 2Experimental Medicine, McGill University, Montreal, Canada; 3Université de Nantes, Nantes, France; 4Montreal Children’s Hospital, McGill University Health Centre, Montreal, Canada; and 5Nutrition Department, Faculty of Medicine, Université de Montréal, Montreal, Canada

Corresponding Author: Ahmad Haidar, Ph.D., Institut de Recherches Cliniques de Montréal 110, avenue des Pins Ouest, Montréal, Québec, Canada H2W 1R7; email address ahmad.haidar@mail.mcgill.ca
Introduction

Advances in insulin pumps and glucose sensors have motivated the development of closed-loop delivery systems. 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.

Delayed insulin absorption would likely hinder the performance of closed-loop systems. 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.

Methods

Participants and Setting
We retrospectively analyzed data collected from 15 closed-loop experiments from a randomized trial 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/m², 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.

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:

\[
\frac{dQ_1(t)}{dt} = u(t) - \frac{Q_1(t)}{t_{max}} \quad \text{where } Q_1(0) = u(0)t_{max} + Q_1
\]

\[
\frac{dQ_2(t)}{dt} = \frac{Q_1(t)}{t_{max}} - \frac{Q_2(t)}{t_{max}} \quad \text{where } Q_2(0) = Q_1(0) + Q_2
\]

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 \(Q_2\). The insulin/glucagon plasma concentration \(C(t)\) is obtained assuming fast equilibration in the plasma space.
Pharmacokinetics of Insulin Aspart and Glucagon in Type 1 Diabetes during Closed-Loop Operation

Haidar

\[ C(t) = \frac{1}{t_{\text{max}}} \frac{Q_2(t)}{w \cdot MCR} \times 10^6 + I_b \]

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. For insulin, an ultrasensitive assay documented that C-peptide secretion persists over decades but decreases with disease duration. A study in 70 type 1 diabetes subjects found that \( I_b \) estimated by the same model also decreased with diabetes duration.

Individual insulin/glucagon pharmacokinetic parameters (\( t_{\text{max}} \), \( MCR \), and \( I_b \)) were estimated using a stochastic modeling approach with WinBUGS version 1.4 and WBDDiff 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.](image1)

![Figure 2. A sample fit of plasma glucagon concentration.](image2)

**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, \( t_{\text{max}} \), were comparable to literature data in type 1 diabetes \([\text{insulin} 51 (19) \text{ min}, \text{glucagon} 19 (4) \text{ min}, \text{mean (standard deviation)}]\). \( t_{\text{max}} \) 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 \([0.019 (0.015–0.026) \text{ liter/kg/min, median (interquartile range)}]\) and was slightly higher than MRC for glucagon \([0.012 (0.010–0.014) \text{ liter/kg/min, median (interquartile range)}]\). Insulin and glucagon \( MCR \) correlated negatively \((r = -0.7; p = .015)\). Table 1 shows the pharmacokinetics parameters of insulin and glucagon. \( t_{\text{max}} \), \( MCR \), 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

<table>
<thead>
<tr>
<th></th>
<th>$t_{max}$</th>
<th>MCR</th>
<th>$I_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin aspart</td>
<td>51 (19) min</td>
<td>0.019 (0.015–0.026) liter/kg/min</td>
<td>10.2 (6.3–15.2) mU/liter</td>
</tr>
<tr>
<td>Glucagon</td>
<td>19 (4) min</td>
<td>0.012 (0.01–0.014) liter/kg/min</td>
<td>50 (45–56) pg/ml</td>
</tr>
<tr>
<td>Correlation between insulin and glucagon parameters</td>
<td>0.7 $^b$</td>
<td>-0.7 $^c$</td>
<td>0.5</td>
</tr>
</tbody>
</table>

$^a$ 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.

During closed loop, patients with slow insulin absorption have an increased risk of hypoglycemia. 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 and is likely to affect glucagon pharmacokinetics. There is also evidence that higher body fat might influence insulin and glucagon action. 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 and Haidar and coauthors). 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 might also incorporate this knowledge in their fixed parameters.

Most pharmacokinetics studies used a noncompartment approach during clamp or postprandial conditions, with fewer studies adopting the compartment approach. 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 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.

Funding:

This work was supported by Diabète Québec, Canadian Diabetes Association (Operating grant OG-1-11-3462-RR) and J-A De Sève Chair held by Rémi Rabasa-Lhoret. Medtronic supplied the pumps and sensors.

Disclosures:

Rémi Rabasa-Lhoret is a consultant for AstraZeneca, Boehringer, Eli Lilly, Merck, Novo-Nordisk, and Sanofi-Aventis; has received grants from AstraZeneca, Eli Lilly, Merck, Novo-Nordisk, and Sanofi-Aventis; and has received speaking fees from AstraZeneca, Eli Lilly, Merck, and Novo-Nordisk.

References:


