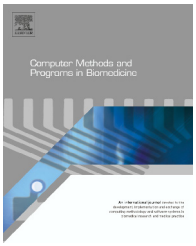
COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 117 (2014) 298–307

journal homepage: www.intl.elsevierhealth.com/journals/cmpb



Pharmacokinetics of insulin lispro in type 2 diabetes during closed-loop insulin delivery

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ARTICLE INFO

Article history:
Received 7 February 2014
Received in revised form 9 July 2014
Accepted 14 July 2014

Keywords:
Pharmacokinetics
Insulin lispro
Artificial pancreas
Type 2 diabetes
Bayesian estimation
Mathematical modelling

ABSTRACT

Insulin pharmacokinetics is not well understood during continuous subcutaneous insulin infusion in type 2 diabetes (T2D). We analyzed data collected in 11 subjects with T2D [6 male, 9 white European and two of Indian ethnicity; age 59.7(12.1) years, BMI 30.1(3.9) kg/m^2, fasting C-peptide 1002.2(365.8) pmol/l, fasting plasma glucose 9.6(2.2) mmol/l, diabetes duration 8.0(6.2) years and HbA1c 8.3(0.8)%; mean(SD)] who underwent a 24-h study investigating closed-loop insulin delivery at the Wellcome Trust Clinical Research Facility, Cambridge, UK. Subcutaneous delivery of insulin lispro was modulated every 15 min according to a model predictive control algorithm. Two complementary insulin assays facilitated discrimination between exogenous (lispro) and endogenous plasma insulin concentrations measured every 15–60 min. Lispro pharmacokinetics was represented by a linear two-compartment model whilst parameters were estimated using a Bayesian approach applying a closed-form model solution. The time-to-peak of lispro absorption (t_{max}) was 109.6 (75.5–120.5) min [median (interquartile range)] and the metabolic clearance rate (MCR_I) 1.26 (0.87–1.56) $\times 10^{-2}$ l/kg/min. MCR_I was negatively correlated with fasting C-peptide ($r_s = -0.84$; $P = .001$) and with fasting plasma insulin concentration ($r_s = -0.79$; $P = .004$). In conclusion, compartmental modelling adequately represents lispro kinetics during continuous subcutaneous insulin infusion in T2D. Fasting plasma C-peptide or fasting insulin may be predictive of lispro metabolic clearance rate in T2D but further investigations are warranted.

1. Introduction

Closed-loop insulin delivery, also known as 'the artificial pancreas' combines a continuous glucose monitoring (CGM) device, a control algorithm, and an insulin pump, and has the potential to transform diabetes care [1,2]. The control algorithm receives, in real-time, sensor glucose concentration and computes the amount of insulin to be delivered by the insulin pump. Clinical trials have demonstrated the safety and efficacy of closed-loop delivery in adults [3], adolescents [4] and pregnant women [5] with type 1 diabetes (T1D). A recent study evaluated closed-loop system in 12 subjects with type 2 diabetes (T2D) [6] in preparation for testing in non-critically ill inpatients with insulin treated T2D [7].

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http://dx.doi.org/10.1016/j.cmpb.2014.07.004
0169-2607/

Computer-based simulations have the capability to accelerate cost-effective development of the artificial pancreas. In an in silico testing environment, alternative study protocols can be tested against competing glucose control algorithms prior to clinical evaluations [8]. A number of in silico environments have been proposed in T1D [9,10] but T2D virtual populations are not documented and would be helpful.

A glucoregulatory model normally comprises a sub-model of insulin kinetics describing absorption of subcutaneously administered insulin. A number of insulin kinetics models have been proposed mostly applying compartmental modelling [11–15]. However, none of the models was identified using clinical data collected during continuous subcutaneous insulin infusion in T2D.

In the present work, we used compartmental modelling to describe absorption of insulin lispro in subjects with T2D who underwent investigations of closed-loop insulin delivery over 24 h [16]. Model parameters were estimated using Bayesian inference [17] by fitting the statistical model to the plasma insulin concentration. We derived a closed-form solution of the compartmental model and integrated it into the statistical model which markedly accelerated the parameter estimation process. We assessed correlations between lispro pharmacokinetics and subjects' demographic data to identify factors predictive of lispro absorption and clearance.

2. Material and methods

2.1. Dataset and experimental design

Insulin-naïve subjects with T2D underwent investigations of closed-loop insulin delivery at the Wellcome Trust Clinical Research Facility, Addenbrooke's Hospital, Cambridge [16]. The study was approved by the Cambridge Research Ethics Committee and subjects signed informed consent prior to the commencement of the study. We analyzed data collected during a 24-h study visit when subjects' usual diabetes treatment (non-insulin glucose-lowering medication) was withheld and was replaced by exogenous insulin [16].

A subcutaneous cannula was inserted in the abdomen for the delivery of insulin lispro (Humalog, Eli Lilly, Indiana) by a study pump (Animas 2020 Johnson&Johnson, NJ) in the morning of the study. A continuous glucose monitoring device (FreeStyle Navigator®, Abbott Diabetes Care, Alameda, CA, USA) informed insulin delivery by the pump using a model-predictive-control algorithm [18]. From 9:00 a.m. on Day 1 until 9:00 a.m. on Day 2, the insulin infusion rate was adjusted every 15 min according to the control algorithm. Three meals of 50, 80 and 60 g carbohydrate were consumed at 9:00 a.m., 1:00 p.m. and 6:00 p.m. (all Day 1), respectively, without administering prandial insulin boluses. Subjects remained sedentary during the study. Blood samples were taken for measuring plasma insulin at the following time points relative to 9:00 a.m. on Day 1: 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 255, 270, 285, 300, 330, 360, 390, 420, 450, 480, 510, 540, 555, 570, 585, 600, 630, 660, 690, 720, 750, 780, 810, 840, 870, 900, 960, 1020, 1080, 1140, 1200, 1260, 1320, 1380 and 1440 min. Blood samples were taken every 15 min to measure plasma glucose.

2.2. Insulin, C-peptide and glucose assay

Samples were centrifuged immediately with plasma kept on ice and stored at −80 °C prior to further analyses. Plasma insulin was measured using two approaches, an immunochemiluminometric assay (Invitron, Monmouth, UK; intra-assay CV 4.7%; inter-assay CV 7.2–8.1%) which has 100% cross reactivity with insulin lispro to quantify total plasma insulin, and AutoDELFIA immunoassay (Perkin Elmer Life Sciences, Wallac Oy, Turku, Finland; inter-assay CV 3.1% at 29 pmol/l, 2.1% at 79.4 pmol/l, 1.9% at 277 pmol/l, 2.0% at 705 pmol/l) which has zero cross reactivity with insulin lispro to quantify endogenous plasma insulin.

Baseline fasting C-peptide was measured by a chemiluminescence immunoassay (Diasorin Liaison XL, Deutschland GmbH, Dietzenbach, Germany; inter-assay CV 5.6% at 563 pmol/l, 4.5% at 2529 pmol/l, 5.8% at 5449 pmol/l).

Plasma glucose was measured by YSI2300 STAT Plus Analyser (YSI, Fleet, Hampshire, UK).

2.3. Insulin kinetics

The kinetics of exogenous insulin was described by a two-compartment model:

$$\frac{di_1(t)}{dt} = -\frac{i_1(t)}{t_{max}} + \frac{u(t)}{60}, \quad i_1(0) = D \tag{1}$$

$$\frac{di_2(t)}{dt} = -\frac{1}{t_{max}}[i_2(t) - i_1(t)], \quad i_2(0) = 0 \tag{2}$$

where $i_1(t)$ and $i_2(t)$ are the amounts of unabsorbed insulin in the subcutaneous insulin depots (U), $u(t)$ denotes the exogenous insulin infusion (U/h), t_{max} is the time-to-peak of insulin absorption (min), and D is a small amount of priming insulin bolus administered at time $t = 0$. The exogenous plasma insulin concentration is obtained assuming instantaneous equilibration between insulin appearance in plasma and plasma insulin reflecting a short plasma insulin half-life relative to the frequency of plasma insulin measurements [19,20]:

$$I_{EXO}(t) = \frac{1000}{t_{max} MCR_I W} i_2(t) \tag{3}$$

where $I_{EXO}(t)$ is the exogenous plasma insulin concentration (mU/l), MCR_I is the metabolic clearance rate of insulin (l/kg/min), and W is subject's weight (kg). t_{max} and MCR_I are individual model parameters.

2.4. Exogenous insulin concentration

Total, exogenous, and endogenous insulin concentrations were related using a linear correction to account for between-assay differences [21]:

$$I_{TOTAL}(t) = I_{EXO}(t) + a + b \times I_{ENDO}(t) \tag{4}$$