Can J Diabetes 41 (2017) 485–490

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Computer Simulation Model to Train Medical Personnel on Glucose Clamp Procedures

Pooya Maghoul MSc [a], Benoit Boulet PhD [a], Annie Tardif BSc [b], Ahmad Haidar PhD [c,*]

[a] Department of Electrical and Computer Engineering, Faculty of Engineering, McGill University, Montreal, Quebec, Canada
[b] Institut de Recherches Cliniques de Montréal, Montreal, Quebec, Canada
[c] Department of Biomedical Engineering, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

ARTICLE INFO

Article history:
Received 24 April 2017
Received in revised form
23 July 2017
Accepted 2 August 2017

Keywords:
computer simulations
glucose clamps
insulin resistance
insulin secretion

ABSTRACT

Objective: A glucose clamp procedure is the most reliable way to quantify insulin pharmacokinetics and pharmacodynamics, but skilled and trained research personnel are required to frequently adjust the glucose infusion rate. A computer environment that simulates glucose clamp experiments can be used for efficient personnel training and development and testing of algorithms for automated glucose clamps.
Methods: We built 17 virtual healthy subjects (mean age, 25±6 years; mean body mass index, 22.2±3 kg/m^2), each comprising a mathematical model of glucose regulation and a unique set of parameters. Each virtual subject simulates plasma glucose and insulin concentrations in response to intravenous insulin and glucose infusions. Each virtual subject provides a unique response, and its parameters were estimated from combined intravenous glucose tolerance test–hyperinsulinemic–euglycemic clamp data using the Bayesian approach. The virtual subjects were validated by comparing their simulated predictions against data from 12 healthy individuals who underwent a hyperglycemic glucose clamp procedure.
Results: Plasma glucose and insulin concentrations were predicted by the virtual subjects in response to glucose infusions determined by a trained research staff performing a simulated hyperglycemic clamp experiment. The total amount of glucose infusion was indifferent between the simulated and the real subjects (85±18 g vs. 83±23 g; p=NS) as well as plasma insulin levels (63±20 mU/L vs. 58±16 mU/L; p=NS).
Conclusions: The virtual subjects can reliably predict glucose needs and plasma insulin profiles during hyperglycemic glucose clamp conditions. These virtual subjects can be used to train personnel to make glucose infusion adjustments during clamp experiments.

Mots clés :
simulations par ordinateur
clampages glycémiques
insulinorésistance
insulinosécrétion

RÉSUMÉ

Objectif : Le clampage glycémique est la technique la plus fiable pour évaluer la pharmacocinétique et la pharmacodynamique de l'insuline, mais un personnel de recherche qualifié et formé est nécessaire pour fréquemment ajuster le débit de perfusion de glucose. Un environnement informatique qui permet de simuler des expériences de clampage glycémique peut favoriser une formation efficace du personnel et servir à la conception et à l'analyse d'algorithmes de clampage glycémique automatisé.
Méthodes : Nous avons créé 17 sujets virtuels en bonne santé (âge moyen, 25±6 ans ; indice de masse corporelle moyenne, 22,2±3 kg/m^2) qui comprennent chacun un modèle mathématique de régulation de la glycémie et un ensemble de paramètres uniques. Chaque sujet virtuel simule des concentrations plasmatiques de glucose et d'insuline en réponse aux perfusions d'insuline et de glucose par voie intraveineuse. Chaque sujet virtuel présente une réponse unique pour laquelle les paramètres étaient estimés à partir de la combinaison des données obtenues lors de l'épreuve de tolérance au glucose par voie intraveineuse et du clampage euglycémique hyperinsulinémique selon l'approche bayésienne. Nous avons validé les sujets virtuels en comparant la simulation de leurs prédictions aux données des 12 individus en bonne santé qui avaient subi un clampage hyperglycémique.

* Address for correspondence: Ahmad Haidar, PhD, Department of Biomedical Engineering, Faculty of Medicine, McGill University, 3775, University Street, Montreal, Quebec H3A 2B4, Canada.
E-mail address: ahmad.haidar@mcgill.ca

1499-2671 © 2017 Canadian Diabetes Association.
The Canadian Diabetes Association is the registered owner of the name Diabetes Canada.
http://dx.doi.org/10.1016/j.jcjd.2017.08.004

Résultats : Les sujets virtuels ont permis d'anticiper les concentrations plasmatiques de glucose et d'insuline à la suite des perfusions de glucose déterminées par le personnel de recherche formé qui réalisait des expériences simulées de clampage hyperglycémique. Ni la quantité totale des perfusions de glucose (85±18 g *vs* 83±23 g ; p=NS) ni les concentrations plasmatiques de l'insuline (63±20 mU/l *vs* 58±16 mU/l ; p=NS) n'étaient différentes entre les sujets simulés et les patients réels.
Conclusions : Les sujets virtuels permettent d'anticiper de manière fiable les besoins en glucose et les profils des concentrations plasmatiques d'insuline durant le clampage hyperglycémique. Ces sujets virtuels peuvent être utilisés pour former le personnel à faire les ajustements de perfusion de glucose durant les expériences de clampage.

Introduction

The glucose clamp procedure is the gold standard for measuring insulin secretion and sensitivity (1). Moreover, the euglycemic glucose clamp procedure is the most reliable way to obtain quantitative information on the pharmacokinetic and glucodynamic properties of insulin preparations (2). It allows the quantitative study of insulin preparations under comparative and reproducible conditions (2).

During glucose clamp procedures after insulin administration, intravenous glucose is infused at a variable rate based on regular plasma glucose measurements to keep the glucose level constant. The total amount of glucose infused reflects the net glucose-lowering effect of the administered insulin. Moreover, the time course of intravenous glucose infusion describes the time course of insulin action. This is the most suitable method for assessing the pharmacokinetic and pharmacodynamics properties of insulin preparations (2).

Determination of appropriate changes to be made in the intravenous glucose infusion rate requires skilled and trained medical personnel. Moreover, if glucose levels are clamped near the hypoglycemia range, determining the right and timely amount of glucose infusion becomes critical for the patient's safety. A computer-based simulation environment that simulates glucose clamp experiments can be used for efficient personnel training and development and testing of algorithms that automate glucose clamps (automatic determination of glucose infusion rates) (3).

Computer simulation environments are constituted of virtual subjects with various characteristics. In this paper, we present an environment of 17 virtual healthy subjects, each comprising a unique mathematical representation. Each virtual subject simulates plasma glucose and plasma insulin concentrations in response to intravenous insulin and glucose infusions, thus allowing the simulation of complex clamp experiments. The virtual subjects' mathematical representations were estimated from combined intravenous glucose tolerance test (IVGTT)–hyperinsulinemic–euglycemic clamp clinical data using the Bayesian approach. The virtual subjects were validated by comparing their simulated predictions against data from 12 healthy individuals who underwent hyperglycemic glucose clamp procedures.

Methods

Mathematical model

The mathematical model comprises 4 subsystems describing insulin secretion, plasma insulin kinetics, insulin action and plasma glucose kinetics. The model takes the time profiles of intravenous insulin and intravenous glucose infusions as inputs and predicts the time profiles of plasma glucose and plasma insulin concentrations. The subsystems are defined as follows.

Plasma insulin kinetics

Plasma insulin kinetics are represented by a 1-compartment subsystem (4):

$$I' = -nI(t) + SR(t) + U(t)/V_1$$

where $I(t)$ (pmol/L) is plasma insulin concentration above basal value, n (L/min) is the constant rate of insulin clearance, $SR(t)$ (pmol/L×L/min) is the pancreatic insulin secretion (above basal) entering the plasma and normalized to the volume of distribution, $U(t)$ (pmol/min) is the rate of exogenous insulin infusion, and V_1 (L/kg) is the insulin distribution volume.

Insulin secretion

Above basal pancreatic insulin secretion entering the plasma, $SR(t)$, is assumed to be controlled by plasma glucose concentration and its rate of change (5):

$$SR(t) = SR_s(t) + SR_d(t)$$

where $SR_s(t)$ is the secretion in response to the plasma glucose concentration (static glucose control) and $SR_d(t)$ is the secretion in response to the rate of change in plasma glucose concentration (dynamic glucose control). $SR_s(t)$ is defined as follows (5):

$$SR_s(t) = Y(t)$$

$$\frac{dY(t)}{dt}(t) = -\alpha\{Y(t) - \beta[G(t) - G_b]\}$$

where α (L/min) and β (L/min) are transfer rate parameters, and G_b (mmol/L) is baseline glucose level. $SR_d(t)$ is related to positive plasma glucose rate of change as follows:

$$SR_d(t) = k_d \frac{dG(t)}{dt} \quad \text{if } \frac{dG(t)}{dt} > 0 \text{ and } G(t) > G_b$$
$$= 0 \quad \text{otherwise}$$

where k_d (pmol.m^{-2}.mmol/L^{-1}) is the effect of the increasing glucose rate of change on insulin secretion.

Insulin action

Insulin action is partitioned into suppression of endogenous glucose production, promotion of glucose disposal and distribution of glucose (6). The effect of insulin lags behind plasma insulin concentrations by 10 to 30 minutes (7), and state variables of the delayed effect of insulin are defined as follows:

$$\frac{dx_1(t)}{dt} = -k_{a1}x_1(t) + k_{a1}S_t I(t)$$

$$\frac{dx_2(t)}{dt} = -k_{a2}x_2(t) + k_{a2}S_d I(t)$$