Mathematical Biosciences 228 (2010) 136–146

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

A three-compartment model of the C-peptide–insulin dynamic during the DIST test

J. Geoffrey Chase [a], Klaus Mayntzhusen [b], Paul D. Docherty [a,*], Steen Andreassen [b], Kirsten A. McAuley [c], Thomas F. Lotz [a], Christopher E. Hann [a]

[a] Department of Mechanical Engineering, University of Canterbury, New Zealand
[b] Centre for Model-based Medical Decision Support, Aalborg University, Aalborg, Denmark
[c] Edgar National Centre for Diabetes Research, University of Otago, Dunedin, New Zealand

ARTICLE INFO

Article history:
Received 8 October 2009
Received in revised form 24 August 2010
Accepted 2 September 2010
Available online 15 September 2010

Keywords:
Insulin sensitivity tests
Compartmental model
Physiological model

ABSTRACT

Dynamic insulin sensitivity (*SI*) tests often utilise model-based parameter estimation. This research analyses the impact of expanding the typically used two-compartment model of insulin and C-peptide kinetics to incorporate a hepatic third compartment. The proposed model requires only four C-peptide assays to simulate endogenous insulin production (*uen*), greatly reducing the cost and clinical burden.

Sixteen subjects participated in 46 dynamic insulin sensitivity tests (DIST). Population kinetic parameters are identified for the new compartment. Results are assessed by model error versus measured data and repeatability of the identified SI.

The median C-peptide error was 0% (IQR: −7.3, 6.7)%. Median insulin error was 7% (IQR: −28.7, 6.3)%. Strong correlation ($r = 0.92$) existed between the SI values of the new model and those from the original two-compartment model. Repeatability in SI was similar between models (new model inter/intra-dose variability 3.6/12.3% original model −8.5/11.3%).

When frequent C-peptide samples may be available, the added hepatic compartment does not offer significant diagnostic, repeatability improvement over the two-compartment model. However, a novel and successful three-compartment modelling strategy was developed which provided accurate estimation of endogenous insulin production and the subsequent SI identification from sparse C-peptide data.

1. Introduction

A wide variety of methods have been used to model insulin kinetics and dynamics, most often to enable the assessment of the efficiency of the hormone for glucose regulation in clinical studies. Various modelling strategies exist on a spectrum between the very simple, single parameter, physiologically relevant modelling [1,2], and highly complex non-physiological multi-variable black or grey box methods [3,4]. Researchers must select the approach that best captures the desired insulin kinetics and/or dynamics with respect to the available data, resolution and noise.

Insulin models are often supplemented with C-peptide data in research studies [5], as C-peptide and insulin are produced in equi-molar amounts. Therefore, C-peptide data can be deconvoluted to re-estimate a piece-wise rate of endogenous insulin secretion ($uen(t)$). Both insulin and C-peptide are cleared by the kidneys at a relatively slow rate, which can be defined using a priori anatomical data (height, weight, sex, age) [5]. Insulin is also cleared by the liver at a comparatively fast and variable rate across subjects [6]. No a priori knowledge has been used to accurately define this hepatic clearance rate. In contrast, C-peptide is not cleared by the liver and thus provides a well-defined, readily available means of accurately defining the endogenous pancreatic secretion of insulin.

Glucose is cleared to cells in the interstitial regions of the body. Thus, to predict insulin sensitivity (*SI*), it is important for a model to accurately predict the insulin concentrations in this compartment. Compounding this issue, insulin is not effectively measurable in the interstitium, although plasma concentrations can be readily obtained.

The most well-known method for modelling the insulin effect on glycaemia is Bergman's minimal model [7]. However, this model has been shown to have some drawbacks in dynamic tests such as the intravenous glucose tolerance test (IVGTT) [8–10]. In particular, it has been demonstrated that the identified glucose disposal parameters can cause interference in the identification method [11].

Thus, most model-based approaches typically use two compartments including a plasma (I) and interstitial (Q) compartment. These models generally incorporate appearance in plasma from all sources and clearance from one or both compartments. Fig. 1 shows four variations of the two-compartment approach capturing the essential aspects of several models published in the literature.

* Corresponding author. Tel.: +64 3 3642987x7224.
E-mail address: paul.docherty@pg.canterbury.ac.nz (P.D. Docherty).

0025-5564/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.mbs.2010.09.001

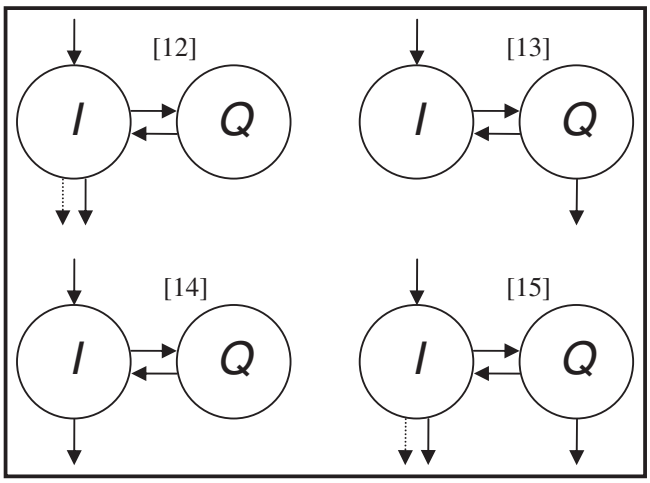

Fig. 1. Two-compartment modelling approaches for insulin [12–15]. (···saturative clearance, — proportional clearance)

Other models use three or more compartments. Generally, these models include a plasma, interstitium (*s* and *f* subscripts denote slow and fast equilibrating, respectively) and hepatic (*H*) and/or circulatory compartment. Three such approaches were presented by Sherwin et al. [16] and are shown in Fig. 2.

The hepatic compartment is included as approximately 80% of insulin clearance can occur in the liver. The potential benefits of the liver compartment include a more physiological treatment of the clearance rate and a transport delay between $uen(t)$ and its eventual impact on the interstitial insulin profile. However, the relatively inaccurate or highly variable estimations of the free volume of the liver [17,18] make it difficult to accurately include the concentration in this compartment. In addition, validating the transport rates between a hepatic compartment and plasma is difficult without direct measurement of the hepatic concentration. Furthermore, population functions or parameters for these rates, similar to those found by Van Cauter et al. for insulin transport rates in and out of plasma [5], are not known. Hence, given also the relatively fast transport observed between the liver and plasma [17] it is often lumped into the plasma compartment to minimise highly variable unknowns despite the loss of direct physiological relevance [16].

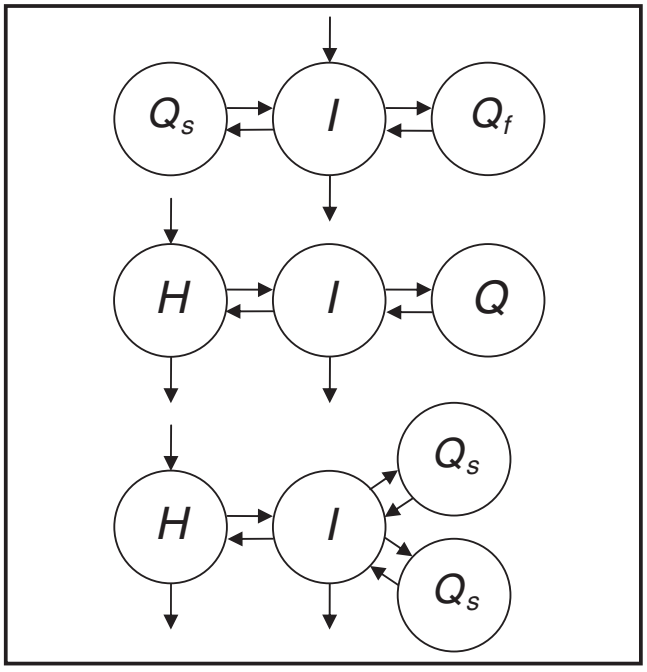

Fig. 2. General approaches to three/four-compartment modelling of insulin dynamics [16].

The research presented here describes a novel three-compartment modelling approach and develops population parameter relationships for the transport rates between the hepatic compartment and plasma. With this approach, the requirement for numerous expensive C-peptide assays can be minimised and the pancreatic output can be defined using four such samples. The kinetic parameters identified using the C-peptide model are directly applied to a three-compartment insulin model due to the similarity in the passive characteristics of the hormones. The model thus incorporates plasma, interstitium and hepatic compartments. The approach is tested and validated using DIST test data obtained by our group and initially presented in Lotz et al. [15,19].

2. Method

2.1. Subjects

There were 46 DIST tests completed on 17 subjects. The study population consisted of 11 individuals with normal glucose tolerance (NGT), 2 with type 2 diabetes (T2DM), and 4 individuals with impaired fasting glucose (IFG). Full subject and protocol details can be found in [15,19].

2.2. Protocol

The dynamic insulin sensitivity test (DIST) is a low-dose insulin-modified IVGTT that samples plasma glucose, insulin and C-peptide in 5–10 min intervals over a 40–50 min test [19]. Subjects sat in an upright position for the duration of the test. A cannula was inserted into the antecubital fossa to enable blood sampling and the administration of insulin and glucose. Blood was sampled at $t = 0, 10, 15, 20, 25, 30, 35, 40, 50$ min with glucose (50% dextrose) and insulin (actrapid) boluses applied immediately after the $t = 10$ and 20 min samples, respectively. Three dosing protocols were used in this pilot study:

- Low dose – 5 g glucose, 0.5 U insulin.
- Medium dose – 10 g glucose, 1 U insulin.
- High dose – 20 g glucose, 2 U insulin.

All blood samples were assayed for glucose (Abbot, Illinois, USA), insulin and C-peptide (Roche Diagnostics, Germany). Each subject was tested 1–3 times with those receiving three tests repeating the medium dose. Specifically, $N = 12$ subjects repeated tests at different dosing, while $N = 8$ subjects had repeated doses.

2.3. Model

The model in this research is an extension of the model used frequently by our group which can be seen in Lotz et al. [15,19] with an added hepatic compartment. Including a hepatic compartment allows localised liver clearance dynamics and more physiological delays between the pancreatic release of insulin and its appearance in the plasma. To avoid problematic estimates of the hepatic distribution volume [17,18], the proposed hepatic compartment is formulated in units of (insulin and C-peptide) mass, rather than concentration. As in [15,19] all other compartments are modelled in terms of concentration. The mathematical formulation is: