Mathematical Biosciences 000 (2016) 1–10

Contents lists available at ScienceDirect

Mathematical Biosciences

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

Insulin kinetics and the Neonatal Intensive Care Insulin–Nutrition–Glucose (NICING) model

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Physiological modelling
Glucose
Insulin
Premature infant
Glycaemic control

ABSTRACT

Background: Models of human glucose–insulin physiology have been developed for a range of uses, with similarly different levels of complexity and accuracy. STAR (Stochastic Targeted) is a model-based approach to glycaemic control. Elevated blood glucose concentrations (hyperglycaemia) are a common complication of stress and prematurity in very premature infants, and have been associated with worsened outcomes and higher mortality. This research identifies and validates the model parameters for model-based glycaemic control in neonatal intensive care.

Methods: C-peptide, plasma insulin, and BG from a cohort of 41 extremely pre-term (median age 27.2 [26.2–28.7] weeks) and very low birth weight infants (median birth weight 839 [735–1000] g) are used alongside C-peptide kinetic models to identify model parameters associated with insulin kinetics in the NICING (Neonatal Intensive Care Insulin–Nutrition–Glucose) model. A literature analysis is used to determine models of kidney clearance and body fluid compartment volumes. The full, final NICING model is validated by fitting the model to a cohort of 160 glucose, insulin, and nutrition data records from extremely premature infants from two different NICUs (neonatal intensive care units).

Results: Six model parameters related to insulin kinetics were identified. The resulting NICING model is more physiologically descriptive than prior model iterations, including clearance pathways of insulin via the liver and kidney, rather than a lumped parameter. In addition, insulin diffusion between plasma and interstitial spaces is evaluated, with differences in distribution volume taken into consideration for each of these spaces. The NICING model was shown to fit clinical data well, with a low model fit error similar to that of previous model iterations.

Conclusions: Insulin kinetic parameters have been identified, and the NICING model is presented for glycaemic control neonatal intensive care. The resulting NICING model is more complex and physiologically relevant, with no loss in bedside-identifiability or ability to capture and predict metabolic dynamics.

1. Introduction

Mathematical models of glucose–insulin physiology have been developed with differing levels of complexity for a wide range of scientific and clinical applications. Models developed for the determination of model-based measures of physiology (e.g. [1,2]), such as insulin sensitivity, tend to be more complex and comprehensive, requiring higher data density and/or measurement of multiple metabolic species. Other models are designed for specific clinical applications, such as glycaemic control in intensive care (e.g. [3–6]), or Type 1 Diabetes cohorts (e.g. [7]). These models tend to be less complex, as metabolic measurements are minimised in clinical or outpatient settings due to clinical and patient factors such as cost, availability, or comfort. In general, physiological models must have appropriate resolution, be mathematically identifiable [8], as well as practically applicable within their chosen application [9].

While glucose–insulin models for adult intensive care applications are more widely documented [9,10] virtually no work has looked at neonatal intensive care unit (NICU) applications. Elevated blood glucose levels (BG) (hyperglycaemia) is a common complication of prematurity and stress in neonatal intensive care, and while definitions and thresholds vary [11], studies show that 30–70% of very/extremely low birth weight infants have at least

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http://dx.doi.org/10.1016/j.mbs.2016.08.006
0025-5564/

one BG > 8 mmol/L [12–16]. Hyperglycaemia is associated with increased mortality [15–17], and morbidity/complications in this cohort [15–21], but there is still debate over whether hyperglycaemia causes increased morbidity, or is reflective of worsened condition.

There is no best practice method for the treatment of hyperglycaemia in this cohort. Use of insulin has been shown to increase glucose tolerance [22–27], resulting in increased weight gain [23,25,27], but also commonly results in increased incidence of hypoglycaemia (low blood glucose concentration) [28–30], which is also dangerous. In adult intensive care even a single hypoglycaemic episode has been associated with increased risk of mortality [31–33], while in neonatal intensive care hypoglycaemia has been associated with adverse neurological outcomes [34,35]. Model-based methods for glycaemic control have been little investigated, due in part to the extremely fragile nature of this cohort and the subsequent limitations on invasive procedures and blood sample collection [36] that thus also limit the ability to identify parameters to validate more physiologically relevant and complex models.

The aim of this study is twofold. First, this paper presents a clinically applicable and physiologically relevant model of glucose–insulin physiology in hyperglycaemic very/extremely premature infants (gestational age < 32 weeks), and secondly it aims to identify insulin kinetic parameters for this model. With regards to the first aim, it combines a previous, simpler, model iteration in this cohort [37] with a more physiologically descriptive model currently utilised for glycaemic control in the adult intensive care unit [5]. Specifically, this model is more descriptive with regards to modelled insulin kinetics and dynamics [38], necessary for safe and effective glycaemic control.

Related to the second aim, this paper also focuses on parameter identification of modelled insulin kinetics. While the key glucose dynamics have been previously published [39,40], this study uses a previously published methodology from adults [41] and a novel data set of C-peptide concentrations from a very low birth weight (<1500 g) cohort to evaluate diffusion of insulin between plasma and the interstitial fluid, and total liver and kidney clearance of insulin. In addition, the assumptions around insulin distribution volumes in the plasma and interstitial compartments are examined, and kidney glomerular filtration rate (GFR) is used to provide a patient specific value for renal clearance of insulin. The revised kinetics model is then used to create a new more physiologically relevant and complex, yet equally identifiable, glucose–insulin model, which is validated using clinical data.

2. Models and methods

2.1. NICING model of glucose–insulin physiology

The NICING (Neonatal Intensive Care Insulin–Nutrition–Glucose) model for glycaemic control in very/extremely preterm neonates is developed from a previous NICU model [37] and the ICING (Intensive Care Insulin–Nutrition–Glucose) model for adult intensive care [5]. The values given, with the exception of those derived in this study, are predominantly derived from literature, and are originally presented and discussed in [37,39].

In the new NICING model, blood glucose ($G \in \mathbb{R} : G \geq 0$), plasma ($I \in \mathbb{R} : I \geq 0$) and peripheral ($Q \in \mathbb{R} : Q \geq 0$) insulin kinetics are described:

$$\dot{G} = -p_G G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P_{ex}(t) + EGP * m_{body} - CNS * m_{brain}}{V_{g,frac}(t) * m_{body}} \quad (1)$$

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I (I(t) - Q(t)) + \frac{u_{ex}(t)}{V_P * m_{body}} + (1 - x_L) u_{en} \quad (2)$$

$$\dot{Q} = n_I \frac{V_P}{V_Q} (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \quad (3)$$

where G has units of mmol/L/min, and I and Q have units of mU/L/min. Clearance of glucose includes both insulin mediated and non-insulin mediated routes. Insulin mediated uptake is modulated by insulin sensitivity ($s_I \in \mathbb{R} : s_I \geq 10^{-7}$), while non-insulin mediated routes include a brain-mass (m_{brain} ~14% whole body mass, m_{body}) dependant [40] central nervous system uptake (CNS = 0.088 mmol/kg/min), and a concentration dependant pathway capturing other glucose clearances such as from the kidney ($p_G = 0.003$/min). As p_G trades off mathematically with S_I and cannot be directly measured in this cohort, the adult value of 0.003/min is assumed. Glucose enters the system via exogenous (P_{ex}) inputs (parenteral and enteral) and endogenous glucose production ($EGP = 0.033$ mmol/kg/min) by the liver [39]. $V_{g,frac}$ is the volume of distribution of glucose in plasma in litres and is based on gestational age [37]. Saturation of insulin mediated glucose uptake in adults is modulated with a Michaelis–Menten function, characterised by the parameter α_G. For neonates no saturation has been observed [42], so this value is $\alpha_G = 0$.

Liver clearance of insulin occurs in two main processes, a first pass hepatic clearance of endogenously secreted insulin (x_L) and clearance of insulin from circulating blood (rate constant: n_L). This hepatic clearance is a receptor-mediated process resulting in saturation of clearance at high insulin concentrations [43,44], and so is modelled with a Michaelis–Menten function, characterised by the parameter α_I. Saturation of liver clearance and first pass hepatic clearance of insulin cannot be measured in premature infants, or indirectly determined in this analysis, so the adult value of $\alpha_I = 0.0017$ L/mU and $x_L = 0.67$ are used [5,45].

Kidney clearance of insulin (rate constant: n_K) includes both glomerular filtration of insulin, and proximal tubal reabsorption. Insulin movement between the plasma and interstitial fluid, (rate constant: n_I) is likely diffusion based, as it is not reported to be saturated [46,47]. Insulin degradation by cells (rate constant: n_C) is a complex, receptor-mediated process. Receptor bound insulin can either be released back into the extracellular fluid space or internalised by the cell [43]. As insulin-binding and insulin-receptor mediated glucose uptake are related, both share the saturation parameter $\alpha_G = 0$. Insulin is secreted (u_{en}) or is exogenously delivered (u_{ex}), with units of mU/min. Insulin secretion can be calculated using C-peptide [48,49], a molecule secreted in equimolar quantities to insulin with simpler clearance kinetics. If C-peptide measurements are not available, insulin secretion is modelled [49,50]:

$$u_{en} = \begin{cases} \max(4.2, -1.5 + 1.9^*G) & \text{if female} \\ \max(2.2, -0.37 + 0.86^*G) & \text{if male} \end{cases} \quad (4)$$

The volume of distribution of plasma insulin is assumed to be the blood plasma volume (V_P). The volume of distribution of insulin in the peripheral compartment is approximated as the interstitial fluid volume (V_Q).

2.2. C-peptide kinetic model

C-peptide is a protein secreted in equimolar quantities with insulin. However, unlike insulin, it is only cleared by the kidney. Therefore, the relatively simple kinetics of C-peptide provide a means to estimate insulin secretion. The well known 2 compartment kinetics model [48] is used due to its overall physiological

Please cite this article as: J.L. Dickson et al., Insulin kinetics and the Neonatal Intensive Care Insulin–Nutrition–Glucose (NICING) model, Mathematical Biosciences (2016), http://dx.doi.org/10.1016/j.mbs.2016.08.006