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Modelling adrenaline secretion during counterregulatory response in Type 1 Diabetes for improved hypoglycaemia prediction

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Abstract: Counterregulatory hormones play an important role in recovery from hypoglycaemia. For this reason, the study of their secretion under hypoglycaemic conditions may be relevant for the prediction of recovery from low glucose episodes. In Type 1 Diabetes Mellitus patients, adrenaline is the first line of counterregulatory hormone response to hypoglycaemia due to the early impairment of glucagon secretion. An adrenaline secretion model to understand its secretion during hypoglycaemia is proposed in this paper, with focus on the analysis of inter-patient variability. Data from hypoglycaemic clamps were used for the model development. Individual and population parameter values estimation was carried out by means of global optimization and Markov Chain Monte Carlo techniques, respectively.

Keywords: Modelling, Biomedical systems, Type 1 Diabetes, Hypoglycaemia, Counterregulation

1. INTRODUCTION

The risk of hypoglycaemia is still a limiting factor of achieving near-normoglycaemia in Type 1 Diabetes Mellitus patients. However, counterregulatory response to hypoglycaemia is often neglected in simulation studies for control strategies design or predictive algorithms for hypoglycaemia prevention. This may lead to underestimated hypoglycaemia recovery and unwanted glycaemic rebounds.

During hypoglycaemia, while the glucose concentration is decreasing, central and peripheral glucose sensors activate mechanisms to elicit the neuroendocrine, autonomic and behavioural response (the so-called counterregulatory response) (Cryer, 2001). In healthy humans, the initial response to prevent a decline in blood glucose concentration is a reduction in endogenous insulin secretion, which begins while plasma glucose concentration is still in the normoglycaemic range, at approximately 80 mg/dL. Glucagon and adrenaline are secreted as glucose levels fall slightly below the normoglycaemic range, at approximately 68 mg/dL (Schwartz et al, 1987; Tesfaye and Seaquist, 2010). Additionally, there is an activation of the autonomic nervous system that increases adrenaline in the circulation. Beyond the reduction of insulin, glucagon plays the primary role in the correction of hypoglycaemia while adrenaline has a secondary role, as shown by experiments in which recovery from acute hypoglycaemia was studied in healthy subjects (Cryer, 2002; Rizza et al, 1979). Glucagon is secreted by pancreatic alpha-cells and acutely raises plasma glucose concentration by stimulating hepatic glucose production via glycogenolysis and gluconeogenesis. Adrenaline acts on alpha and beta adrenergic receptors at multiple end organs to effect a more sustained increase in plasma glucose concentration: adrenaline increases hepatic glycogenolysis and gluconeogenesis; reduces insulin secretion while increasing glucagon release from the pancreatic islets; reduces glucose uptake and utilization and increases glycolysis by muscle; and, in addition, increases lipolysis in adipose tissue (Cryer et al, 2003). Increased secretion of growth hormone and cortisol also contributes to the response to hypoglycaemia. However, these two hormones do not have an immediate role in the recovery from hypoglycaemia (Cryer et al, 1987), as they are mainly involved in the reaction to prolonged hypoglycaemia (Cryer and Gerich, 1985; Cryer, 2001).

In Type 1 Diabetes, counterregulatory response to hypoglycaemia is impaired. Firstly, due to exogenous insulin therapy, patients with Type 1 Diabetes cannot reduce systemic insulin levels as blood glucose concentrations begin to decline, unless an artificial pancreas or sensor-augmented pump is used (with the inherent limitations of subcutaneous insulin delivery). Thus, subjects with Type 1 Diabetes lack the first line of defence against hypoglycaemia. Secondly, glucagon secretion in response to hypoglycaemia is lost soon after the onset of the disease. Thirdly, the response of adrenaline to a given level of hypoglycaemia is blunted and

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the glycaemic threshold for its secretion is shifted to lower plasma glucose concentration (Amiel et al, 1988; Cryer et al, 2003), together with reduced autonomic symptoms. Nevertheless, due to the absence of endogenous insulin and glucagon response, adrenaline becomes the main actor of the counterregulatory response to hypoglycaemia in Type 1 Diabetes.

To date, few works have partially included counterregulatory response in prediction or simulation models for a more accurate description of hypoglycaemia episodes and time-course recovery from them. A main difficulty is the quantification of counterregulatory plasma hormonal concentrations. Kovatchev et al (1999), presented a mathematical model of insulin-glucose dynamics that included estimates for the onset and rate of counterregulatory responses. They used plasma adrenaline concentrations to validate model results, as they showed high correlation with counterregulation rates. More recently, Dalla Man et al (2014) have included in the latest version of the UVA/PADOVA Type 1 Diabetes Simulator an improved description of glucose kinetics in hypoglycaemia. They have incorporated glucagon secretion and action, as well as a paradoxical increment of glucose utilization during hypoglycaemia.

In this manuscript a mathematical model of adrenaline secretion during hypoglycaemia is presented, as a first step towards modelling of the counterregulatory response in Type 1 Diabetes. The paper is organised as follows: Section 2 presents the structure of proposed mathematical model, the algorithms used to estimate parameters and the methods to evaluate the model; Section 3 shows the results of parameter estimation and goodness of fit; conclusions are drawn in Section 4.

2. METHODS

2.1 Dataset

Data from a eu-hypoglycaemic clamp study was used. Fourteen subjects with Type 1 Diabetes mellitus were enrolled in the study performed at the Clinic University Hospital of Valencia, Spain. Each individual participated in two eu-hypoglycaemic clamp studies with different levels of insulinemia (0.3 mU/Kg/min vs. 1 mU/Kg/min). In an initial phase glucose was normalized to 90 mg/dL by using a variable i.v. insulin infusion. Then a hypoglycaemic plateau at 50 mg/dL was induced for 45 minutes with previous and subsequent phases of euglycaemia. Total duration of the study was 8.5 hours. Plasma glucose was measured every five minutes (YSI 2300, YSI Incorporated Life Sciences, Yellow Springs, Ohio, USA). Plasma adrenaline concentration was measured every 30 minutes due to blood sampling limitations.

2.2 Mathematical model

Figure 1 represents a typical response for adrenaline in our dataset after data interpolation. Adrenaline secretion presents a biphasic nature: the first phase is a quick response against hypoglycaemia that starts when glycaemia is lower than a given threshold; the late phase is associated to the recovery presenting different dynamics. Adrenaline concentration remains constant at basal values until counterregulatory response begins.

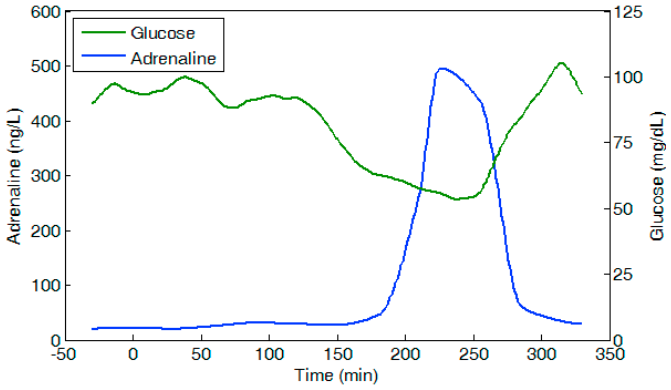

Fig. 1. Example of adrenaline response to hypoglycaemia.

A parallel-input compartmental model is proposed to describe this behaviour, with equations:

$$\dot{Q}_1(t) = -k_{a1} \cdot Q_1(t) + \beta_1 \cdot u(t) \quad (1)$$

$$\dot{Q}_2(t) = k_{a1}(Q_1(t) - Q_2(t)) \quad (2)$$

$$\dot{Q}_3(t) = k_{a1} \cdot Q_2(t) - k_e \cdot Q_3(t) + k_{a2} \cdot Q_4(t) \quad (3)$$

$$\dot{Q}_4(t) = -k_{a2} \cdot Q_4(t) + \beta_2 \cdot u(t) \quad (4)$$

$$u(t) = \begin{cases} 0 & G(t) \geq G_{th} \\ G(t) - G_{th} & G(t) < G_{th} \end{cases} \quad (5)$$

$$A(t) = Q_3(t)/V + A_{basal} \quad (6)$$

$$Q_1(0) = Q_2(0) = Q_3(0) = Q_4(0) = 0;$$

where A(t) is plasma adrenaline concentration (ng/L); A_{basal} is basal adrenaline concentration (ng/L); V is the distribution volume of adrenaline (L); G(t) is plasma glucose concentration (mg/dL); G_{th} is the glucose concentration value that activates the counterregulatory response of adrenaline; u(t) is the model input corresponding to glucose deviation from the activation threshold G_{th} (glucose does not affect adrenaline secretion when above this threshold); $Q_3(t)$ is the measurement compartment of adrenaline mass; rest of compartments, $Q_1(t)$, $Q_2(t)$ and $Q_4(t)$, define the dynamics of each secretion phase (second and first order, respectively); β_1 and β_2 represent the gain of physiological response; k_{a1} and k_{a2} are transfer rate constants between compartments; and k_e is adrenaline rate of disappearance.

Figure 2 depicts the model structure corresponding to equations (1)-(6).