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Qualitative analysis of subcutaneous Lispro and regular insulin injections for stress hyperglycemia: A pilot numerical study

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HIGHLIGHTS

- We model the glucose–insulin feedback system to study stress hyperglycemia.
- Short acting subcutaneous Lispro and regular insulin injections are simulated.
- The resulting glucose variability after insulin injections is analyzed and compared.
- Regular insulin has the lowest glucose variability profile.
- Lispro is more prone to cause hypoglycemia than regular insulin when the subject is not receiving nutrition.

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ABSTRACT

Increased glucose variability (GV) is an independent risk factor for mortality in the critically ill; unfortunately, the optimal insulin therapy that minimizes GV is not known. We simulate the glucose–insulin feedback system to study how stress hyperglycemia (SH) states, taken to be a non-uniform group of physiologic disorders with varying insulin resistance (IR) and similar levels of hyperglycemia, respond to the type and dose of subcutaneous (SQ) insulin. Two groups of 100 virtual patients are studied: those receiving and those not receiving continuous enteral feeds. Stress hyperglycemia was facilitated by doubling the gluconeogenesis rate and IR was stepwise varied from a borderline to a high value. Lispro and regular insulin were simulated with dosages that ranged from 0 to 6 units; the resulting GV was analyzed after each insulin injection. The numerical model used consists of a set of non-linear differential equations with two time delays and five adjustable parameters. The results show that regular insulin decreased GV in both patient groups and rarely caused hypoglycemia. With continuous enteral feeds and borderline to mild IR, Lispro showed minimal effect on GV; however, rebound hyperglycemia that increased GV occurred when the IR was moderate to high. Without a nutritional source, Lispro worsened GV through frequent hypoglycemia episodes as the injection dose increased. The inferior performance of Lispro is a result of its rapid absorption profile; half of its duration of action is similar to the glucose ultradian period. Clinical trials are needed to examine whether these numerical results represent the glucose–insulin dynamics that occur in intensive care units, and if such dynamics are present, their clinical effects should be evaluated.

1. Introduction

In 2001, a study by Van den Berghe changed the intensive care unit (ICU) practice of hyperglycemia management around the world (Van den Berghe et al., 2001). Traditionally, efforts were made to keep blood glucose concentrations below 200 mg/dl; however, Van den Berghe showed that tight glycemic control (TGC) between 80 and 110 mg/dl reduces a patient's morbidity and mortality. The improved outcomes led to an increase in the number of ICUs that adopted a TGC policy (Lowery and Badawi, 2013). The initial optimism, however, was followed by concerns regarding the universal applicability of this treatment, as new trials, including one from the original Van den Berghe group (Van den Berghe et al., 2006), did not corroborate the initial findings. Several trials and meta-analyses that followed demonstrated a significant risk associated with TGC resulting from hypoglycemia and increased GV (Wiener et al., 2008; Finfer et al., 2009; Griesdale et al., 2009). Currently, the glycemic control pendulum has swung back toward a higher initial glucose concentration of 150 mg/dl before insulin therapy is initiated (Jacobi et al., 2012).

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Insulin infusions are generally recommended to treat hyperglycemia in the ICU; however, subcutaneous insulin injections are still used by some providers in critical care because of their ease of use for the nursing staff and the requirement for relatively infrequent blood draws from the patient.

One recent landmark randomized controlled trial that reported increased mortality with TGC in ICU patients was the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation trial (Finfer et al., 2009). This large, prospective, study of adult medical and surgical ICU patients showed that aggressive glucose control may actually increase overall mortality rates, although two subgroups seemed to show a benefit: patients receiving steroids and trauma patients. Defining higher glucose concentrations as acceptable, however, is not necessarily much safer since hyperglycemia, hypoglycemia, and increased GV have similar associated mortality risks (Badawi et al., 2012). In fact, increased GV is itself an independent risk factor associated with hospital mortality in the critically ill (Egi et al., 2006; Ali et al., 2008; Dossett et al., 2008; Krinsley, 2008; Hermanides et al., 2010). The mechanism is not well understood, but in vitro studies have shown that acute fluctuations of glucose can induce endothelial cell damage and apoptosis; this may be one reason by which GV confers worse outcomes (Risso et al., 2001; Quagliaro et al., 2003).

A critical reading of the published literature concerning insulin therapies in intensive care indicates that different patient populations have variable responses to the same insulin treatment (Jacobi et al., 2012); thus, there may not be a single best insulin protocol for the treatment of SH. Future design of clinical trials may then be aided by an improved understanding of how a non-uniform group of physiologic disorders, each producing similar levels of hyperglycemia, would respond to exogenous insulin. One technique that could help provide such insight is to mathematically model the glucose–insulin axis, simulate various SQ insulin therapies, and examine the resultant GV. One modeling approach explicitly incorporates two time delays that exist in the glucose–insulin system. One time delay is due to processes inside the pancreas: β-cells release insulin due to stimulation from glucose. This physiological action requires a certain time for the newly synthesized insulin, or "remote insulin", to cross the endothelial barrier before it can be released. The other time delay represents the effect of insulin on hepatic glucose production; although insulin regulates the liver in a direct fashion, its effect occurs over several minutes. These two time delays are an important reason why the glucose–insulin feedback system is able to sustain ultradian oscillations (Li et al., 2006; Li and Kuang, 2007).

The models may be used to qualitatively compare SQ insulin therapies for the treatment of SH in an ICU setting. Two commonly used SQ insulin products are Lispro and regular insulin. Lispro, an insulin analogue, has a quick 5–15 min onset of action and peaks in 30–90 min with an effective duration of only 4–6 h (Hirsch, 2005a). This type of insulin was designed to treat diabetics enjoying a food bolus. The resulting peak in endogenous insulin levels after a meal has a similar time duration to Lispro; hence, Lispro tends to lower glucose levels in diabetics more effectively than regular insulin. Another advantage of Lispro's short duration of action is that "insulin stacking" (a second insulin injection being given while insulin absorption continues from the previous injection) is thought to be minimized. Regular insulin, in contrast, has an onset of action of about 30 min and peaks in 2–3 h with a longer effective duration of 6–8 h (Hirsch, 2005a).

To our knowledge, there has been no clinical or numerical study that compares SQ Lispro and regular insulin therapy for SH in the critically ill; using numerical simulation to examine such a comparison is the main focus of this paper. The paper is organized as follows: Section 2 contains a description of the mathematical model and the numerical methods used. Stress hyperglycemia is commonly a combination of increased gluconeogenesis and IR; insulin resistance is a common adaptive responsive seen in several patient groups, such as post abdominal surgical patients (Thorell et al., 1994), trauma patients (Black et al., 1982), and those suffering from sepsis (Gump et al., 1974; Andersen et al., 2004). The numerical model consists of a set of non-linear differential equations with two time delays; these equations have been used to study insulin therapy for diabetics with variable IR. Stress hyperglycemia is produced by doubling the amplitude of the function representing glucose production by the liver and adding the effects of varying levels of IR. Functions representing SQ Lispro and regular insulin injections are used to perturb the system at a glucose concentration maximum; the resulting GV is then analyzed. Glucose variability is defined as the average difference between adjacent glucose local maximum (or peaks) and local minimum (or troughs) across each ultradian oscillation. The simulation results are presented in Section 3, which is followed by a discussion in Section 4. A conclusion in Section 5 finishes the paper.

2. Glucose–insulin axis model and numerical methods

In the last few decades, several mathematical models have been proposed and studied with the aim of better understanding the dynamics of the glucose–insulin axis so that safer and more effective insulin administration practices could be developed to treat diabetes mellitus (Li et al., 2006; Li and Kuang, 2007; Bennett and Gourley, 2004a,b; Della Man et al., 2002; Doran et al., 2005; Engelborghs et al., 2001; Mukhopadhyay et al., 2004; Palumbo et al., 2007; Sturis et al., 1991; Tolic et al., 2000; Wang and Li, 2007; Wilinska et al., 2005; Wang et al., 2009; Chen and Tsai, 2010; Wu et al., 2011). The field has a rich history surveyed in reviews (Makroglou et al., 2006, 2011; Palumbo et al., 2013). These methods can be modified to model the effects of SQ insulin when used for SH in the ICU. The types of insulin therapies studied in this paper are restricted to those that would administer SQ injections of either Lispro or regular insulin; the term SQ will henceforth be dropped as an insulin injection descriptor.

The particular model used here (extensively studied in Chen and Tsai, 2010) defines $G(t)$ and $I(t)$ to be the glucose and insulin concentration at time $t \geq 0$, respectively. Mass conservation implies

$$\partial_t G(t) = \{G_p(t) - G_u(t)\} : \quad \text{glucose production} - \text{glucose utilization}, \tag{2.1a}$$

$$\partial_t I(t) = \{I_p(t) - I_c(t)\} : \quad \text{insulin production} - \text{insulin clearance}, \tag{2.1b}$$

where

$$G_p(t) = G_{in}(t) + f_5(I(t-\tau_2)) \times f_6(G(t)), \tag{2.2a}$$

$$G_u(t) = f_2(G(t)) + \beta \times f_3(G(t)) \times f_4(I(t)) + f_7(G(t) - 330), \tag{2.2b}$$

$$I_p(t) = I_{in}(t) + \alpha \times f_1(G(t-\tau_1)), \tag{2.2c}$$

$$I_c(t) = d_i I(t). \tag{2.2d}$$

The functions f_i, where $i = 1 \to 7$, describe the body's glucose production and utilization, as well as insulin production and clearance; $G_{in}(t)$ in Eq. (2.2a) denotes glucose absorption from either enteral nutrition or an intravenous source. Insulin absorption from an exogenous source is represented by $I_{in}(t)$ in Eq. (2.2d). Each of the f_i functions will be discussed next; they have been determined from work that defines some of the key aspects of glucose and insulin metabolism in function form. References to the