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Evaluating modifications to the Glucosafe decision support system for tight glycemic control in the ICU using virtual patients

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ABSTRACT

Intensive insulin therapy has previously shown reduced mortality with lowering blood glucose to between 4.4 and 6.1 mmol/l. However presumably due to fear of hypoglycemia the current recommended glycemic target is 7.8–10 mmol/l. This study evaluates the effect of modifications to the Glucosafe system on the glycemic outcomes of an in silico cohort and which modifications are necessary to lower mean blood glucose under 6.1 mmol/l without hypoglycemic incidents. Based on data from 12 real patients from a previous clinical trial, 12 virtual patients were constructed, the groups were compared and results of the modifications evaluated. Results indicate that virtual patients are applicable in evaluating modifications to advice generation, and that it is possible to lower mean blood glucose below 6.1 mmol/l, with no hypoglycemic incidents. In some patients increased insulin use did not achieve this and decreasing nutritional intake was necessary.

1. Introduction

Hyperglycemia is common in patients hospitalized for critical illness, trauma or after surgery, and has been associated with increased morbidity and mortality [1,2]. Intensive insulin therapy has been tested as a means to achieve glycemic control [3,4] and the Glucosafe system was developed to provide decision support for control of stress hyperglycemia in the intensive care unit (ICU). The Glucosafe system consists of two modules. The first module is a mathematical model of glucose metabolism [5], which can be used to simulate and predict future blood glucose (BG) concentrations. The second module of Glucosafe is used for generating advice [6].

The advice generator provides advice in the form of suggestions for the next doses of insulin and nutrition to be administered to the patient. The advice generator evaluates the effect that different suggestions have on the predicted future BG using the metabolic model. The optimal advice is the advice that gives the most desirable outcome over the next four hours in terms of predicted BG, insulin dose and nutritional intake. To decide which amount of nutrition and insulin, as well as the predicted four-hour BG profile constitutes the "most desirable" outcome, the advice generator uses a set of penalty functions [6].

The landmark study of Van den Berghe et al. [3] used intensive insulin therapy to target a BG range of 4.4–6.1 mmol/l. A mean morning BG of 5.7 mmol/l was achieved, but this also resulted in 5% of patients experiencing hypoglycemic incidents (BG < 2.2 mmol/l). The study showed an 42% reduction in mortality, but presumably due to the fear of hypoglycemia which have been shown to be an independent risk factor for mortality [7,8], higher BG targets (7.8–10 mmol/l) have since been recommended by the American Association of Clinical Endocrinologists and by the American Diabetes Association [9].

The Glucosafe system has twice previously been tested clinically for its ability to lower BG without inducing hypoglycemic incidents. In both studies Glucosafe targeted a BG of 5.5 mmol/l. In the first study a mean BG of 7.0 mmol/l (±1.1 mmol/l) was achieved, significantly lower than in the 24 hour pre- and post-intervention periods [10]. In the second study a mean BG of 7.0 mmol/l (±1.19 mmol/l), significantly lower than the control group, was achieved [11]. Despite these promising results, neither trial successfully achieved a mean BG for the respective cohorts in the 4.4–6.1 mmol/l band and the authors suggested the penalty functions for advice generation be adjusted [10].

The target BG of 5.5 mmol/l was not achieved by Glucosafe, because the goal of a BG of 5.5 mmol/l conflicts with the reluctance to give large doses of insulin and with the reluctance to underfeed the patients. The balance between BG, insulin and nutritional goals is expressed through the penalty functions (see Section 2) and a further reduction in BG could therefore be achieved by

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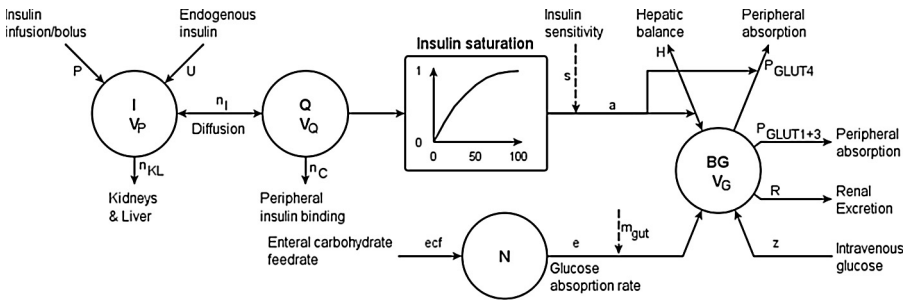

Fig. 1. A simplified diagram of the Glucosafe glucose–insulin model for BG prediction. Solid arrows represent flow and turnover rates, dashed arrows represent effects of variables or parameters on other variables.

reducing the penalty associated with large insulin doses, reducing the penalty associated with underfeeding or both. Evidence supports that managing BG by permissive underfeeding [12] may be a clinically acceptable alternative or supplement to large insulin doses. As the study by Van den Berghe resulted in a greatly lowered mortality and as Glucosafe seems able to lower BG without hypoglycemic incidents, there is reason to reconsider clinical trials with low BG targets. Therefore there is a need to determine which penalty functions, if any, will allow Glucosafe to lower BG into the 4.4–6.1 mmol/l band.

In this study we will investigate if virtual patients [13], derived from real patient data, can be used to suggest modifications to the penalty functions used by the Glucosafe advice generator. We will run the Glucosafe system on virtual patients to determine the modifications of the penalty functions required to reduce the average BG for the virtual patients to within the band of 4.4–6.1 mmol/l.

Provided the model has good predictive accuracy, then this should also apply to real patients. As previous evaluations have shown that Glucosafe has good predictive accuracy, irrespective of the BG level and for different insulin and nutrition regimes. This indicates that the modifications determined from the virtual patients may be used as a reasonable starting point for a subsequent clinical trial.

2. Methods

2.1. The Glucosafe model

A diagram of the Glucosafe model is shown in Fig. 1. Glucosafe models plasma insulin and peripheral insulin concentrations from the endogenous production and exogenous infusions of insulin and the removal of insulin by the kidneys and by insulin degradation in the liver and peripheral tissue. The insulin sensitivity scales the effect of insulin on hepatic removal and peripheral absorption of glucose. BG is modeled from insulin-dependent and insulin-independent removal and glucose from nutrition and intravenous infusions [5]. Details of the model and equations can be found in Appendix A.

2.2. Insulin sensitivity

Glucosafe estimates patient-specific insulin sensitivities from data on nutrition, insulin consumption, and BG concentrations. This insulin sensitivity is a dimensionless parameter where values close to one indicate a normal, non-impaired response to insulin and lower values indicate insulin resistance. In the model the estimated insulin sensitivity is assumed to be a time-varying, patient-specific parameter, which is independent of the treatment the patient is receiving. Every time a new BG measurement is entered into Glucosafe, the insulin sensitivity is estimated, and used in the prediction of BG until a new measurement is entered and the insulin sensitivity is re-estimated. As Glucosafe cannot predict the changes in insulin sensitivity it assumes the insulin sensitivity does not change between measurements but only when estimated from a new BG measurement. An example of an insulin sensitivity profile is given in Fig. 2.

2.3. Penalty functions

For advice generation, Glucosafe uses four penalty functions. Penalties are based on total amount of nutrition, amount of enteral nutrition, insulin dosage, and the resulting predicted BG. A grid search minimizes the sum of these penalties to present the optimal advice on nutrition and insulin use. The following provides a short description of the penalty functions. The rationale for the shapes of the functions has previously been described [6]. The shape and scaling of the penalty functions initially used in this study are identical to the penalty functions used during the data collection [10,11].

2.3.1. Glycemic penalty

The penalty is for the predicted BG, resulting from the recommended nutrition and insulin use. The penalty (Fig. 4A) is defined as:

$$f_G(G) = \left(\ln\left(\frac{G}{G_0}\right)\right)^2 \times P_G \quad (1)$$

where G is the predicted BG, $G_0 = 5.5$ mmol/l is the specific BG where the penalty is zero, and $P_G = 22.6$ is a dimensionless scaling factor. The BG penalty used is the mean of penalties calculated from the predicted BG at 1, 2, 3, and 4 h.

2.3.2. Insulin dose penalty

To decrease the use of excessive insulin doses the use is penalized with the following function (Fig. 4B):

$$f_I(P) = \left(\frac{(P \times C \times K_m)^2}{K_m^2} - 1\right) \times P_I \quad (2)$$

where P is the insulin infusion rate (mU/(kg min), $C = 98.1$ kg/min l is a factor for converting insulin infusion rate to plasma concentra-

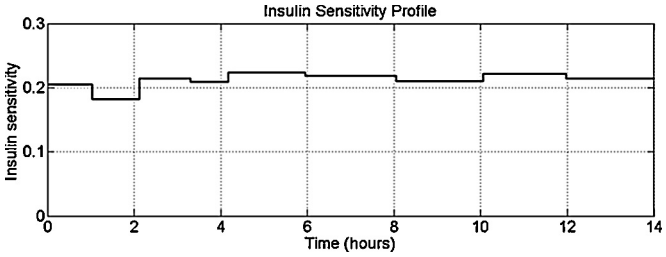

Fig. 2. Example of a 14 h insulin sensitivity profile from a patient. Recalculation of, and subsequent change in, insulin sensitivity occurs whenever a new BG measurement is entered into the Glucosafe system.