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Factors affecting the success of glucagon delivered during an automated closed-loop system in type 1 diabetes

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ABSTRACT

Background: In bi-hormonal closed-loop systems for treatment of diabetes, glucagon sometimes fails to prevent hypoglycemia. We evaluated glucagon responses during several closed-loop studies to determine factors, such as gain factors, responsible for glucagon success and failure.
Methods: We extracted data from four closed-loop studies, examining blood glucose excursions over the 50 min after each glucagon dose and defining hypoglycemic failure as glucose values < 60 mg/dl. Secondly, we evaluated hyperglycemic excursions within the same period, where glucose was > 180 mg/dl. We evaluated several factors for association with rates of hypoglycemic failure or hyperglycemic excursion. These factors included age, weight, HbA1c, duration of diabetes, gender, automation of glucagon delivery, glucagon dose, proportional and derivative errors (PE and DE), insulin on board (IOB), night vs. day delivery, and point sensor accuracy.
Results: We analyzed a total of 251 glucagon deliveries during 59 closed-loop experiments performed on 48 subjects. Glucagon successfully maintained glucose within target (60–180 mg/dl) in 195 (78%) of instances with 40 (16%) hypoglycemic failures and 16 (6%) hyperglycemic excursions. A multivariate logistic regression model identified PE ($p < 0.001$), DE ($p < 0.001$), and IOB ($p < 0.001$) as significant determinants of success in terms of avoiding hypoglycemia. Using a model of glucagon absorption and action, simulations suggested that the success rate for glucagon would be improved by giving an additional 0.8 μg/kg.
Conclusion: We conclude that glucagon fails to prevent hypoglycemia when it is given at a low glucose threshold and when glucose is falling steeply. We also confirm that high IOB significantly increases the risk for glucagon failures. Tuning of glucagon subsystem parameters may help reduce this risk.

1. Introduction

While intensive treatment of type 1 diabetes is associated with improvement in the hemoglobin A1c and decreased risk of long-term complications (Anon, 2000, 2003), it increases the risk of hypoglycemia (Kumareswaran, Evans, & Hovorka, 2012; Anon, 1997). Commercially available glucagon is effective in treating hypoglycemia (Aman & Wranne, 1988), but it is not approved for use in preventing hypoglycemia. Additionally, the dose (1 mg) is supra-physiologic and may be associated with rebound hyperglycemia. Smaller doses of glucagon may be sufficient to treat mild or impending hypoglycemia when given manually (Hartley, Thomsett, & Cotterill, 2006; Haymond & Schreiner, 2001) as well as in a closed-loop system (Castle et al., 2010).

Insulin pump therapy for type 1 diabetes has become commonplace in medicine today, with the move towards automated insulin infusion via closed-loop system being the natural next step forward (Elleri, Dunger, & Hovorka, 2011; Hovorka, 2011). Most closed-loop systems only deliver the hormone insulin (Bakhtiani, Zhao, El Youssef, Castle, & Ward, 2013; Bergenstal et al., 2013). Suspension of insulin delivery in anticipation of hypoglycemia ('low glucose suspend' systems, e.g. Paradigm® Veo™) has proven quite useful for reducing hypoglycemia (Garg et al., 2012) however, the slow absorption of insulin from the subcutaneous space makes prediction of glucose trends difficult, and withholding insulin alone may not be sufficient to prevent hypoglycemia (Castle, Engle, El Youssef, Massoud, & Ward, 2010). Kadish first proposed dual hormone use in 1964 (Kadish, 1964), and then more recently several investigators in the field of closed-loop systems have developed bi-hormonal systems with both insulin and glucagon (Castle, Engle, El Youssef, Massoud, Yuen, et al.,

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2010; El-Khatib, Russell, Nathan, Sutherlin, & Damiano, 2010; Haidar et al., 2013; Van Bon et al., 2012; van Bon et al., 2014). These studies have shown that small subcutaneous doses of glucagon help reduce the incidence and duration of hypoglycemia.

Our group uses an indirect adaptive proportional–derivative (APD) controller to calculate subcutaneous delivery rates of insulin and glucagon (El Youssef et al., 2011). Proportional and derivative gain factors used to determine insulin and glucagon delivery rates in the fading memory proportional derivative (FMPD) system, the precursor to the APD, were initially determined during animal studies (Gopakumaran et al., 2005). Castle et al. showed that glucagon delivery using high-gain parameters ("front loading") was more effective than low-gain parameters in reducing the frequency of hypoglycemia (Castle, Engle, El Youssef, Massoud, Yuen, et al., 2010). In the ideal situation, control algorithms should calculate a sufficient glucagon dose to keep blood glucose within the normal range — not to overshoot (causing hyperglycemia) or to undershoot (failing to prevent hypoglycemia).

Additionally, there are other factors that can affect the glycemic response of glucagon (Russell, El-Khatib, Nathan, & Damiano, 2010). It is well known that glucagon is the counter-regulatory hormone to insulin, but when insulin-on-board (IOB) is high, the effect of glucagon may be blunted, or even absent altogether (Castle, Engle, El Youssef, Massoud, & Ward, 2010; Russell et al., 2010; Cherrington et al., 1976). Glucagon raises blood glucose by glycogenolysis and its response can be affected by glycogen stores in the liver. Potentially, the effect of glucagon may be blunted if the glycogen stores in the liver are low such as in fasting states.

Unlike with insulin, there are few available glucagon absorption and action models based on subcutaneous delivery (Lv, Breton, & Farhy, 2013) and one of the concerns about using glucagon in a bi-hormonal system is the antagonistic behavior between insulin and glucagon. It is possible that, if the glucagon delivery gain factors are set too high, unstable oscillation between hypo and hyperglycemia could occur. For this reason, we aim to maximize the effect of glucagon in preventing hypoglycemia while minimizing subsequent rebound hyperglycemia.

The primary aim of this paper is to elucidate factors that determine the likelihood of glucagon success when given in small doses in bi-hormonal closed-loop systems. The secondary aim is to determine the effect of the current gain factors used to calculate glucagon doses within our control algorithm on the risk of failure, and to tune the algorithm to improve the success rate.

2. Methods

2.1. Studies

We extracted data from four studies performed by our group in Portland OR, looking at blood and sensor glucose excursions after doses of glucagon are given. A total of 48 subjects underwent 59 closed-loop studies. We reviewed all patient sessions, whether or not the study was completed. Subject data obtained included age, weight, diabetes duration, and HbA1c. These studies were performed at Oregon Health and Science University and Legacy hospitals (both Portland, OR) between 2009 and 2013, after receiving approval from the respective review boards (see Table 1). The algorithm used to calculate glucagon delivery was exactly the same in all studies (El Youssef et al., 2011), except that in the first study, glucagon doses were not scaled based on the estimated IOB. Glucagon was given via a manually controlled syringe pump (Medfusion 2001) in the first two studies, while it was automatically delivered via an insulin pump (Omnipod system, Insulet, Bedford, MA) loaded with glucagon in the last two studies.

2.2. Data extraction

We evaluated all subcutaneous deliveries of glucagon during these closed-loop studies along with the glucose response. Sensor glucose was measured every 5 min during all four studies, while blood glucose was measured every 10 min during glucagon vs. placebo (GvP) and steroid studies (SS), every hour during the day and every two hours during the night for the in-patient (IP) study, and every two hours during the day and every three hours during night for the out-patient (OP) study. In this paper we analyzed sensor glucose over 50 min after glucagon injection to determine success or failure, and we included an assessment of the relative difference between blood and sensor glucose values whenever both were available. A window of 50 min was used because the APD control algorithm uses a 50-min refractory period for glucagon after a threshold dose was delivered. This threshold dose varies from a lower limit of 0.4 μg/kg to an upper limit of 2.0 μg/kg, based on the current calculated IOB (up to an IOB of 20% of the subject's total daily insulin requirement), and represents the maximum allowed dose of glucagon during the last 50 mins of closed-loop running. Failure of glucagon to prevent hypoglycemia was defined by a fall in glucose levels below 60 mg/dl during the 50-min window, while a hyperglycemic excursion was defined as a rise in glucose levels above 180 mg/dl during the same window. A hypoglycemic failure took precedence over a hyperglycemic excursion within the 50-min window, such that only one of the two could be defined per instance of glucagon delivery. Additionally, we separated instances of glucagon delivery based on whether a single dose was given or multiple doses were given before the refractory period was activated (multiple doses could have been given during the 50 min period if the first glucagon delivery did not reach the maximum dose allowed within 50 min). The algorithm uses exponentially-decaying weighted estimates of the PE and DE over the prior 15 and 10 min respectively (PE weight $= 0.3$, DE weight $= 0.4\ \mathrm{min}^{-1}$), along with preset gain factors for the error terms (PE gain $= -2.7$, DE gain $= -0.6$), to calculate glucagon doses (Gopakumaran et al., 2005). The gain factors are negative since the glucagon subsystem is activated in reverse to the insulin subsystem, i.e. when glucose is below the target, the weighted PE is negative, and when glucose is falling, the weighted DE is negative. Multiplying a negative gain factor with a negative PE or DE value would yield positive glucagon infusion rates in these circumstances, and the

Table 1
Characteristics of the four studies reviewed (G = glucose values 50 min after glucagon dose).

Study Description	Subjects (male)	Experiments (Automated Y = yes, N = no)	Glucagon Deliveries	Successful Deliveries ($60 \le G \le 180$)	Hypoglycemia ($G < 60$)	Hyperglycemia ($G > 180$)
Glucagon vs. Placebo (GvP): a study of glucagon vs. placebo using a modified PID system (FMPD) in a closed-loop setting.	10 (5)	10 (N)	54	47	4	3
Steroid Study (SS): a study comparing the response of an adaptive system (APD) vs. FMPD to changes in insulin sensitivity with oral steroids.	14 (9)	25 (N)	102	63	30	9
In-patient Study (IP): an in-patient study of an automated version of the APD system described in (Jacobs et al., 2011, 2014)	13 (6)	13 (Y)	65	56	6	3
Out-patient Study (OP): an out-patient, hotel study using the automated APD system.	11 (2)	11 (Y)	30	29	0	1