Efficacy Determinants of Subcutaneous Microdose Glucagon during Closed-Loop Control

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Abstract

Background:

During a previous clinical trial of a closed-loop blood glucose (BG) control system that administered insulin and microdose glucagon subcutaneously, glucagon was not uniformly effective in preventing hypoglycemia (BG <70 mg/dl). After a global adjustment of control algorithm parameters used to model insulin absorption and clearance to more closely match insulin pharmacokinetic (PK) parameters observed in the study cohort, administration of glucagon by the control system was more effective in preventing hypoglycemia. We evaluated the role of plasma insulin and plasma glucagon levels in determining whether glucagon was effective in preventing hypoglycemia.

Methods:

We identified and analyzed 36 episodes during which glucagon was given and categorized them as either successful or unsuccessful in preventing hypoglycemia.

Results:

In 20 of the 36 episodes, glucagon administration prevented hypoglycemia. In the remaining 16, BG fell below 70 mg/dl (12 of the 16 occurred during experiments performed before PK parameters were adjusted). The (dimensionless) levels of plasma insulin (normalized relative to each subject's baseline insulin level) were significantly higher during episodes ending in hypoglycemia (5.2 versus 3.7 times the baseline insulin level, $p = .01$). The relative error in the control algorithm's online estimate of the instantaneous plasma insulin level was also higher during episodes ending in hypoglycemia (50 versus 30%, $p = .003$), as were the peak plasma glucagon levels (183 versus 116 pg/ml, $p = .007$, normal range 50–150 pg/ml) and mean plasma glucagon levels (142 versus 75 pg/ml, $p = .02$). Relative to mean plasma insulin levels, mean plasma glucagon levels tended to be 59% higher during episodes ending in hypoglycemia, although this result was not found to be statistically significant ($p = .14$). The rate of BG descent was also significantly greater during episodes ending in hypoglycemia (1.5 versus 1.0 mg/dl/min, $p = .02$).

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Abstract cont.

Conclusions:

Microdose glucagon administration was relatively ineffective in preventing hypoglycemia when plasma insulin levels exceeded the controller's online estimate by >60%. After the algorithm PK parameters were globally adjusted, insulin dosing was more conservative and microdose glucagon administration was very effective in reducing hypoglycemia while maintaining normal plasma glucagon levels. Improvements in the accuracy of the controller's online estimate of plasma insulin levels could be achieved if ultrarapid-acting insulin formulations could be developed with faster absorption and less intra- and intersubject variability than the current insulin analogs available today.

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