Journal of Diabetes Science and Technology
Volume 2, Issue 4, July 2008

MEETING PROCEEDINGS

Glucose Sensing Issues for the Artificial Pancreas

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Abstract

The first retrospective continuous glucose monitor entered the market in 1999. Now that this tool gives online data, the question arises whether it is ready to be incorporated into a closed-loop system. The author discusses the following questions: (1) Is the accuracy of current continuous glucose monitoring (CGM) systems good enough for use in a prototype artificial pancreas system?; (2) How do we assess CGM accuracy?; (3) What is the minimal distance between a continuous glucose monitor and an insulin delivery site in which a CGM can function accurately?; and (4) Does any physiological and instrumental delay associated with continuous glucose monitoring hamper the development of an artificial pancreas?

J Diabetes Sci Technol 2008;2(4):732-734

The first trial investigating the impact of a continuous glucose monitor with online data on accepted diabetes-related intermediate endpoints, the GuardControl trial, makes one long for more. The Guardian® REAL-Time continuous glucose monitoring (CGM) system (Medtronic, Sylmar, CA) was studied in 162 patients for 3 months in a three-arm, randomized clinical trial. Continuous use of the Guardian REAL-Time lowered HbA1c by 0.6% more than in the control group, while the intermittent use group showed an HbA1c-lowering in between, not significantly different from the control group. Notably, hypoglycemia rates were not reported.[1]

Afterward, presentation of Sensor Augmented Pump Therapy: Results of the First Treat-To-Target Study at the 2007 American Diabetes Association Scientific Sessions put our feet on the ground again. In this study, 138 experienced pump users with type 1 diabetes were randomized to either continuation of current treatment or use of the Paradigm® REAL-Time (RT) System (Medtronic, Northridge, CA) for 6 months. The Paradigm RT platform combines an insulin pump and a continuous glucose monitor with wireless communication from the sensor to the pump. HbA1c was lowered to the same extent in both treatment groups. Although twice as many patients ended with an HbA1c below 7% in the Paradigm RT group, these must by definition be counterbalanced by more patients ending with higher HbA1c levels, as mean HbA1c at endpoint was the same in both groups. Severe hypoglycemia was seen more often in the Paradigm RT group, in part explained by putting the sensor off at critical time points, and one patient with undiagnosed Addison's disease contributing events in the intervention group. Area under the curve in the hypoglycemic range was lower in the intervention group.[2] Intensive treatment in the conventional group—telephone contact once per 2

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Abbreviations: (CGM) continuous glucose monitoring, (HbA1c) hemoglobin A1c, (RT) real time

Keywords: artificial pancreas, closed loop, continuous glucose monitoring

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weeks, unlikely to reflect clinical reality other than during pregnancy—most likely contributed to the minimal contrast in results between the groups. However, one may also argue that improved sensor accuracy is needed for CGM to result in improvement in clinically relevant outcome measures. Support for this line of reasoning also comes from an indirect comparison of home blood glucose meters and CGM. Chen *et al*. from the U.S. Food and Drug Adminstration studied the accuracy of four home blood glucose meters. Three meters showed similar good results and one performed poorly. The three meters showed values in zone A of the Clarke Error Grid at around 97%, while the poor meter showed 74% of values in this zone.[3] This is similar to the accuracy we reported in 2005 in a head-to-head comparison of two CGM systems, with 72 and 76% of values in zone A.[4] So when the use of accurate home blood glucose meters still leaves many patients with insufficient glycemic control, are CGM systems with far less accuracy likely to improve overall glycemic control? Of course, subgroups of patients benefit from this generation of CGM systems, but from a scientific point of view, they should be identified more thoroughly.

How do we evaluate the accuracy of CGM systems? Currently, three methods are in use: field testing, the glucose clamp method, and the meal test with delayed insulin administration. All these methods aim to ensure enough data in the hypoglycemic range, where performance of CGM is critical and generally worse than in the euglycemic range. Worse performance in the hypoglycemic range was reported in a 2007 field trial of the Paradigm RT, with mean absolute difference roughly twice as high in the hypoglycemic range as compared to the euglycemic range.[5] This corresponds well to results obtained with the meal test with delayed insulin administration.[4] In contrast, a head-to-head clamp study of three CGM systems showed similar accuracy in the hypo- and euglycemic range in two systems, and paradoxically better performance in the hypoglycemic range in one system.[6] Further studies are needed to assess the validity of the glucose clamp method when evaluating CGM accuracy.

What is the minimal distance from a continuous glucose monitor at which insulin can be infused? The Graz group was the first to do some investigations in this area.[7] At the 5th Annual Diabetes Technology Meeting in 2005, they showed a stable relationship between blood glucose concentration and the glucose levels at the tissue site of insulin infusion in five healthy volunteers, using an in-house made microperfusion probe.[8] Our group showed that insulin infusion at a distance of 9 mm from a commercially available microdialysis CGM did not influence CGM accuracy in ten patients with type 1 diabetes.[9] Taken together, both investigations indicate that insulin delivery and glucose sensing can be performed concomitantly at the same adipose tissue site.

A fundamental question posed by Hovorka was whether the subcutaneous-subcutaneous approach for the closed-loop system can ever be realized given its inherent delays.[10] Time to blood peak levels of rapid-acting insulin analogs injected subcutaneously is around 50 minutes. The physiological delay between receptor activation and insulin production is about 30 minutes. Delay between plasma and interstitial glucose is estimated to be from 0 to 30 minutes, averaged at 10 minutes. This adds up to 90 minutes plus any instrumental lag of the continuous glucose monitor. There are possibilities to shorten this delay. Peak insulin levels after injection of VIAject™ (Biodel Inc., Danbury, CT) human insulin with additives to enhance absorption, takes 33 rather than 50 minutes.[11] Thus, the major insulin-producing pharmaceutical companies are reminded that development of rapid-acting analogs is not completed. Major efforts may hopefully result in even faster absorption. As to the delay between interstitial and plasma glucose, we recently found no delay. This was assessed with a mealtime test with delayed insulin absorption described above. For statistical analysis, we used curve fitting with horizontal shifting to assess delay.[12] Many studies reporting longer delays applied an acute increase in glucose, and used first order kinetics modeling. Thus, they may not have been able to dissect distribution time from a possible delay between plasma and interstitium. Finally, instrumental delay for some of the continuous glucose monitors is already close to 0 minutes. Taking all this together, overall delay may be brought down from 90+ to 50 minutes, 30 of which are physiological. Whether this will allow for a useful closed-loop system still needs to be determined, but the time seems right for prototype testing first in the clinical research center and then at home.

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