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Clinical equipoise: an argument for expedited approval of the first small step toward an autonomous artificial pancreas

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"Clinical equipoise demands that for the performance of a clinical trial to be ethical, there has to be a state of genuine scientific uncertainty in the medical community over whether a drug or treatment will be beneficial. In this case, no uncertainty exists in the diabetic community that it makes no sense to keep pumping insulin into a patient who is hypoglycemic if there is a simple and safe way to temporarily suspend the basal insulin infusion."

A series of technological advances over the past 30 years have greatly expanded the functionality of insulin pumps beyond that of the original devices, which were basically motorized syringes with plungers that pushed insulin under the skin at a fixed basal infusion rate and that could give separate meal-time boluses of insulin. By contrast, today's 'smart' insulin pumps contain minicomputers that:

- Allow preprogramming of different basal rate profiles for weekdays and weekends;
- Calculate the number of units of insulin that should be needed to cover the amount of carbohydrate the patient estimates in the meal;
- Calculate correction doses to bring high glucose levels back into range and automatically adjust this estimate, if a previous correction dose was recently given to prevent stacking of insulin boluses.

The pump's memory function also keeps records of the insulin doses that have been administered, the carbohydrate intake and the blood glucose levels that have been entered into the dose calculator. These functions provide clinicians with extremely important data to monitor their patients' therapy, especially when caring for adolescents with Type 1 diabetes (T1D) who are notoriously inconsistent in taking premeal bolus doses of insulin. Current pumps can even assist the patients in remembering to take meal boluses by sounding 'reminder alarms' at meal times.

The introduction of real-time continuous glucose monitoring systems (RT-CGM) more than 10 years ago offered the potential to revolutionize the treatment of T1D, especially when used in combination with smart insulin pumps in 'sensor-augmented pump systems.' Glucose sensor data reporting nocturnal glucose profiles would allow clinicians to more fully exploit the variable basal rate capabilities of insulin pumps, and retrospective analysis of postprandial glycemic excursions would assist in determining and adjusting carbohydrate to insulin ratios and correction doses. Real-time sensor data and hypo- and hyperglycemic alarms would give patients the opportunity to make corrections on the fly rather than having to wait for the next regularly scheduled blood glucose meter test. Although it seemed intuitively obvious that a perfect, nonintrusive, accurate and easy-to-use device would be of great

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benefit to patients, the benefits of the early, imperfect RT-CGM systems were more challenging to demonstrate.

As we reviewed in this journal last year, improvements in RT-CGM technology have paved the way for a series of randomized clinical trials in patients with T1D aimed at gathering the evidence regarding the actual benefits of continuous glucose monitoring systems (CGM) [1]. Statistically significant and clinically important improvements in metabolic control of T1D were achieved with RT-CGM only if patients used the CGM devices on a nearly daily basis. Unfortunately, the difficulties involved in using current CGM devices made it challenging to achieve consistent patient use of CGM in clinical trials, particularly in adolescents and younger children, and even more difficult to translate the benefits of CGM into clinical practice.

Severe hypoglycemia, leading to loss of consciousness and seizures, is the acute complication of T1D treatment that is most feared by patients. Although CMGs use lowered glucose and A1c levels without the expected increase in the rate of severe hypoglycemia in subjects with elevated baseline A1c, and reduced time spent in hypoglycemia in subjects with baseline A1c levels already at target, differences in severe hypoglycemia rates were not demonstrated [2,3].

> "Statistically significant and clinically important improvements in metabolic control of Type 1 diabetes were achieved with real-time continuous glucose monitoring systems only if patients used the continuous glucose monitoring system devices on a nearly daily basis."

The Medtronic MiniMed Paradigm® (Medtronic MiniMed, Northridge, CA, USA) is the only currently available integrated sensor-augmented pump (iSAP) system in which the sensor data are transmitted directly to a receiver built into the insulin pump, but the patient remains the 'computer' that has to analyze the data, which are then used for making treatment decisions. Even with iSAP, the risk of severe hypoglycemia did not differ from that in controls using multiple daily injection therapy and blood glucose meter monitoring [4], confirming the belief that no treatment of T1D will ever eliminate the risk of severe hypoglycemia in very well-controlled patients until there is a closed-loop system that automatically controls insulin delivery rates based on RT-CGM. All three elements of an artificial pancreas system (insulin pumps, RT-CGM and controller algorithms to regulate insulin delivery) are already available, and the drive to develop such systems has helped to forge partnerships between academic clinical investigators, NIH and the Juvenile Diabetes Research Foundation and industry.

The main obstacle that must be overcome before closed-loop systems become a practical reality for the treatment of T1D at home is to have redundant safeguards in place that will prevent the overdelivery of insulin due to a system malfunction. Although automatically turning up insulin delivery to prevent hyperglycemia presents a potentially devastating safety risk, turning off a pump for a relatively short period of time to limit the extent and duration of hypoglycemia presents an attractive and arguably safer first step along the pathway to an artificial pancreas. Medtronic has taken that step with the Veo™ pump, which automatically suspends the basal infusion of insulin for up to 2 h when the patient's glucose sensor level crosses a low-glucose threshold and the patient does not respond to the system alarm. Other iSAP systems with low-glucose suspend (LGS) features are in the pipeline.

Several lines of evidence indicate that incorporation of LGS capability into an iSAP system would be particularly useful in lowering the risk of seizures and other severe hypoglycemia events, especially while the patient is asleep during the night, the period of the day with the highest risk for severe hypoglycemia. Night time poses a triple threat for hypoglycemia for our patients due to the loss of plasma epinephrine responses to hypoglycemia during deep sleep, the delayed glucose-lowering effects of antecedent exercise from the prior afternoon, and fixed doses of insulin delivered during the night. It is especially noteworthy that a recent case series described four T1D patients who were wearing a CGM on a night in which they had a hypoglycemic seizure [5]. In each case, low sensor glucose levels preceded the seizure for several hours, providing a window for an LGS-equipped device to prevent the seizure by automatically suspending the basal insulin infusion. Years ago, our group at Yale University (CT, USA) demonstrated that interrupting an insulin pump's basal infusion for 2 h in the middle of the night was associated with a modest rise in blood glucose without any meaningful increase in serum β-hydroxybutyrate levels [6]. Moreover, patients with T1D regularly disconnect their pumps for up to 2 h for exercise [7] and other activities without any adverse consequences.

Unlike regulatory authorities in Australia, Canada and Europe, the US FDA has not yet approved the sale of LGS-equipped pumps in the USA. One reason why the agency did not quickly approve this safety feature of an iSAP system is that RT-CGM is currently approved only as an adjunct to blood glucose meter monitoring, meaning that a high or low sensor glucose value should be confirmed by a meter test before the patient takes corrective action. By contrast, with a LGS pump, an abnormally low sensor reading triggers a corrective action (i.e., suspending the basal rate for up to 2 h), and it does so without the patient being aware of the suspension.

Another reason why the FDA's approval of LGS-enabled pumps has been delayed is the agency's insistence on clinical trial data showing efficacy. Such trials will undoubtedly be difficult to carry out and hard to interpret because the frequency of seizure and coma events due to the failure in responding to RT-CGM alarms in the control group using a pump without LGS capability is likely to be extremely low. Perhaps an even more important question is whether holding up approval of LGS-enabled pumps due to the lack of efficacy data from clinical trials is ethically justified.

The principle of clinical equipoise provides a compelling argument for expedited approval of this first small step toward an autonomous artificial pancreas. Clinical equipoise demands that for the performance of a clinical trial to be ethical, there has to be a state of genuine scientific uncertainty in the medical community over whether a drug or treatment will be beneficial. In this case,

no uncertainty exists in the diabetic community that it makes no sense to keep pumping insulin into a patient who is hypoglycemic if there is a simple and safe way to temporarily suspend the basal insulin infusion. The wisdom of expediting the approval of LGS by foreign regulatory agencies without clinical trial data has been demonstrated by recent clinical use studies of this system from centers in Germany, the UK and Australia. In these studies, LGS was shown to be well accepted by patients and to be safe and effective in reducing the duration of hypoglycemia without resulting in an increase in hyperglycemia [8,9]. In the absence of safety concerns, would it not also be better to let clinicians and patients in the USA decide whether LGS is beneficial? This way, we could move on to the next step of using LGS to prevent hypoglycemic events by suspending the basal insulin infusion based on a rapid rate of fall of sensor glucose levels [10–12].

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