EDITORIAL

Reducing Hypoglycemia in Type 1 Diabetes: An Incremental Step Forward

Irl B. Hirsch, MD

CONTINUOUS SUBCUTANEOUS INSULIN infusion (CSII) (insulin pump) has been available for more than 30 years—slightly less than a third of the 92 years that insulin has been available. The concept behind CSII was that smaller depots of insulin would allow more consistent insulin absorption, resulting not only in less hypoglycemic exposure but also in a reduction of severe hypoglycemia. Although one meta-analysis confirmed this advantage,¹ a more recent meta-analysis did not.² This has added uncertainty to our original premise about this therapy.

Regardless of how insulin is delivered, we have long known that using glucose data to make diet and insulin decisions is critical. This has been shown for home blood glucose monitoring, where more frequent testing is strongly associated with lower hemoglobin A1c (A1C) levels.³ With continuous glucose monitoring (CGM), it is not surprising that the increase in data often results in better diabetes control, but this technology, like any other, is only effective when used properly.⁴ It is important that CGM has been shown to reduce overall hypoglycemic exposure in well-controlled type 1 diabetes,⁵ but corresponding reductions in severe hypoglycemia have not been documented with CGM, in part because of excluding subjects experiencing severe hypoglycemia in these studies.

The idea of using a sensor-augmented pump (SAP)—effectively combining CSII and CGM—to reduce severe hypoglycemia is attractive, but thus far the end result has resolved the problem of neither severe hypoglycemia nor, in particular, devastating nocturnal hypoglycemia. This is partly due to the relatively long kinetics of our modern-day prandial insulins.⁶ The “tail” from a late dinnertime bolus can last well into the night, resulting in a high-risk situation for the patient. One idea would be to automatically suspend insulin delivery so that at a minimum basal insulinemia could be reduced during the critical first few minutes of the hypoglycemia without resulting in hyperglycemia or diabetic ketoacidosis. For this to be effective, the CGM device would have to be accurate at hypoglycemic levels to suspend at the appropriate times.

It is therefore both reassuring and exciting that suspending at threshold levels with SAP was recently shown to reduce nocturnal hypoglycemic exposure and event rates by 38% and

32%, respectively.⁷ It is surprising that the median duration of suspension during these nocturnal events was only 11.9 min. Only 19.6% of suspend events lasted for the maximum time allowed of 2 h (with the threshold for suspension set at 70 mg/dL for most of the subjects) with a subsequent mean glucose level after the 2-h suspend of 92.6 mg/dL. Furthermore, in this 3-month study there were no episodes of severe hypoglycemia with the threshold suspend with SAP system, whereas there were four episodes with the SAP alone.

Why is this study reassuring? It needs to be appreciated there are significant numbers of skeptical academic and clinical diabetologists, regulators, and, yes, payers who questioned if the current technology is robust enough to show improvements in one of the most important Achilles’ heels of type 1 diabetes therapy, nocturnal hypoglycemia.

For those of us who have watched (and lived) this therapy since its inception, it is exciting to see that threshold suspend with SAP is safe, does not cause rebound hyperglycemia, and is the next step for the technological holy grail of an automated closed-loop pancreas (“bionic pancreas”).

But before we celebrate too much the publication of this trial, important limitations need to be acknowledged. First, this was a short trial, and the reduction of hypoglycemia over time is not known. Second, similar benefits in adolescents and young adults (or a geriatric population) cannot be extrapolated (even though the small number of adolescents and young adults included in this study subset data analysis showed similar benefits). Finally, we don’t know how the threshold suspend with SAP would fare in a population prone to hypoglycemia but with significantly higher A1C levels. This is an important population, as significant numbers of patients with high A1C levels using CSII have high rates of severe hypoglycemia.⁸ The authors also point out that the sensor values could not be validated by a reference method, which is understandable in a home study.

Despite these caveats, we continue to learn more about the dangers of hypoglycemia. For example, it was recently reported that there is a bidirectional association between dementia and hypoglycemia.⁹ This is in addition to all of the neurological and cardiac concerns that are well described.¹⁰ Any incremental benefit to reduce hypoglycemic exposure is obviously welcomed.

Although the eventual goal is a closed-loop system, the advances to date have been driven by many organizations, but perhaps none has done more than Medtronic Minimed Diabetes (Northridge, CA). The closed-loop system has support with funded grants from the JDRF, the National Institutes of Health, and Diabetes UK, but Medtronic Diabetes has pushed to secure this first incremental step. The concern, of course, is that as this technology evolves it will be available to only a limited population with resources, as opposed to the large number of people who could actually benefit. We will need to consider what will most likely be a complex cost-benefit analysis to better understand how important a further reduction of hypoglycemia exposure may be. This analysis needs to be more sophisticated than a "bean-counter" assessing the number of emergency room visits. Rather, we need to take into account all aspects of hypoglycemia, including those that are not always appreciated. For example, 12% of patients with type 1 diabetes over the age of 50 years have a hypoglycemic-related seizure or coma *per year*.⁸ These life-threatening episodes are often treated at home and therefore do not add the same large financial cost to the system as an emergency room visit, ambulance ride, or hospital admission.

In the near term, our hope is that a threshold suspend system will be available in the United States later this year, which will have a meaningful impact in preventing hypoglycemia, especially nocturnal. This can only occur with more physicians being trained on how to best implement the system and with a better economic model than we've used for real-time CGM. This last barrier will require input from our professional societies, it is hoped with more success than we've seen in the past. Nevertheless, the prospect of this technology moving to a more automated system, eventually resulting in a closed-loop device, is finally gaining momentum.

References

1. Pickup JC, Sutton AJ: Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 2008;25:765–774.
2. Yeh H-C, Brown TT, Mauruthur N, Ranasinghe P, Berger Z, Suh YD, Wilson LM, Haberl EB, Brick J, Bass EB, Golden SH: Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med* 2012; 157:336–347.
3. Miller KM, Beck RW, Bergenstal RM, Goland RS, Haller MJ, McGill JB, Rodriguez H, Simmons JH, Hirsch IB: T1D Exchange Clinic Network: Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1C levels in T1D Exchange Clinic Registry participants. *Diabetes Care* 2013 February 1 [Epub ahead of print].
4. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group: Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. *Diabetes Care* 2009;32:1947–1953.
5. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group: The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383.
6. Hirsch IB: Insulin analogues. *N Engl J Med* 2005;352: 174–183.
7. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, Ahmann AJ, Welsh JB, Lee SW, Kaufman FR, for the ASPIRE In-Home Study Group: Threshold-based insulin pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013 June 22 [Epub ahead of print]. doi: 10.1056/NEJMoa1303576.
8. Hirsch IB: Insulin delivery in the T1D Exchange Clinic Registry: Factors associated with pump use, discontinuation, and clinical outcomes. [Oral presentation, February 10, 2012, Session 17.] In: *The 5th International Conference on Advanced Technologies & Treatments for Diabetes, Barcelona, Spain* (program book, p 21). www.kenes.com/attd.
9. Yaffe K, Falvey CM, Hamilton N, Harris TB, Simonsick EM, Strotmeyer ES, Shorr RI, Metti A, Schwartz AV; Health ABC Study: Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. *JAMA Intern Med* 2013 June 10 [Epub ahead of print]. doi: 10.1001/jamainternmed.2013.6176.
10. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R: Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384–1395.

Address correspondence to:

Irl B. Hirsch, MD
University of Washington School of Medicine
4225 Roosevelt Way NE, Suite 101
Seattle, WA 98105

E-mail: ihirsch@uw.edu