COMMENTARY

Insulin Infusion Sets and Continuous Glucose Monitoring Sensors: Where the Artificial Pancreas Meets the Patient

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THE PAST YEAR has seen dramatic advancement in the field of technology for the treatment of type 1 diabetes (T1D) highlighted by the commercial approval of the first artificial pancreas (AP) system, as well as the recent food and drug administration approval of nonadjunctive dosing from continuous glucose monitoring (CGM) in open loop continuous subcutaneous insulin infusion (CSII) pump or multiple daily injection therapy.^{1,2} Clinical research on AP systems has advanced from highly controlled 1–2 week trials to minimally supervised outpatient studies of 3–6 months' duration.^{3–6} Future generations of AP technology are already under clinical trial investigation, including the ongoing studies for features such as adaptive learning, fully closed loop functionality, exercise detection integration, and dual hormone systems.^{7–13} As AP systems advance to the standard of care for clinical practice over the next few years, research data suggest that patients will experience a reduction in hemoglobin A1c along with reduction in hypoglycemia. However, this improvement in care is likely to increase reliance on technology for the management of diabetes and necessitates that patients continuously wear a CGM sensor and insulin infusion set (IIS).

In this issue of *Diabetes Technology and Therapeutics*, Ward, et al. present preclinical results on a comprehensive series of CGM studies focused on the development of a single site combined IIS and CGM sensor device.¹⁴ The need to wear two separate devices when conducting sensor augmented pump or AP therapy has been frequently raised as a barrier by patients in clinical care and during research studies. Previously held assumptions about combined devices have reasoned that measuring glucose at the insulin delivery site will result in inaccurate CGM values due to the local effects of insulin. This particular assumption has been challenged by numerous clinical studies which have failed to consistently find such a local bias.^{15,16} In this article, Ward and colleagues describe the construction of a combined IIS/CGM sensor whereby the CGM electrode is laminated to the outer wall of the insulin delivery cannula creating a single insulin delivery and CGM device.

The authors go on to describe a series of experiments both in vitro and in vivo in which rapid acting insulin, saline

solution, and nothing were infused through two different versions of a combined IIS/CGM sensor. Initial in vitro experiments revealed that with a standard H₂O₂ sensor set at 600 mV, exposure to rapid acting insulin caused a large sensor artifact resulting in subsequent irreversible damage to the sensor (termed electrode poisoning). Further in vitro work revealed that the electrode poisoning was due not to the presence of the insulin, but to certain phenolic preservatives (phenol and m-cresol) used in the preparation of the rapid acting insulins. The authors then tested a second type of sensor, a redox mediator-type sensor, set at 175 mV. Use of a lower bias potential (175 mV vs. 600 mV) avoided the phenolic artifact seen at higher potentials. When used in vivo, the redox-mediated sensors showed a similar sensing signal pattern during insulin delivery as was shown during delivery of saline and with only the device present. These findings reveal that the bias in sensing during insulin delivery is likely avoidable using a sensor which operates at a lower voltage. The findings from this preclinical trial are noteworthy not only because the authors show in vivo success of an interference-free IIS/CGM sensor site but also because of the investigation of the interfering substances and attempts to control for the impact of fluid, sensor, and insulin presence in the results.

Several other groups have also reported trials of combined IIS/CGM sensor devices, with varying outcomes. Rumpler, et al. recently reported results of such a device during in vitro and human in vivo studies.¹⁷ Rumpler's in vitro studies showed a very strong linear correlation ($R^2=0.998$) between the CGM and reference glucose value in the range of 0–300 mg/dL. The human-use studies showed a mean absolute relative difference (MARD) of 22.5% with a consensus error grid (CEG) analysis^{18,19} showing 87% of values in zone A+B. Norgaard, et al. have reported results for the MiniMed Duo in 45 patients with T1D.²⁰ They reported a MARD of 15.5% with >95% of values in the CEG zone A+B range. These accuracy results are somewhat worse than those seen for separate CGM sensors currently on the market in the United States and Europe.^{21,22}

Beyond simply combining the IIS and CGM sensor into one site, additional barriers to improve on-body elements

remain. These include the need to prolong IIS life beyond 3 days to better match to the CGM sensor life of 7–14 days and the need to address IIS failures and occlusions. IIS failure results in rapid development of hyperglycemia and, if not addressed, will progress to potentially life-threatening diabetic ketoacidosis (DKA). Current IIS's are approved for 3 days of use, and studies on the potential life span of these devices have shown that while some IIS's may last for up to 7 days, mean survival is about 4–6 days regardless of IIS material (steel vs. Teflon), with rising glucose values after day 3 of continuous use.^{23,24} The reason for IIS failures remains somewhat unclear as local reactions around the IIS (bioincompatibility) may play a larger role than simple kinking, as various studies show differing rates of bioincompatibility with different IIS materials.²⁵ Authors have also described IIS failure in the absence of a pump alert as a “silent occlusion.” A novel side-port IIS is being developed to lessen the incidence of silent occlusions, and its use has been shown to reduce silent occlusions by up to 75%.²⁶

Additional mitigation of the risk of IIS failure and subsequent DKA may be achieved by improved real-time detection of IIS failure through automated analysis of CGM data using fault detection algorithms.^{27,28} Engineering-based fault detection algorithms developed by Bequette, et al. use “sliding windows” of glucose averages over time to detect abnormal glucose levels relative to the patient's baseline level of glycemic control. These are accumulated into a glucose fault metric which can be utilized by a CSII or AP system to alert a patient to likely IIS failure. Fault detection systems inherently rely on CGM readings and thus development of combined IIS/CGM sensor devices which enable a patient to continually wear both devices may additionally help to detect failure of these devices.

Advances in diabetes technology show substantial promise to improve glycemic control, reduce hypoglycemia, and decrease the burden of managing diabetes. Central to this technology is the need for patients to continuously wear both an IIS and CGM sensor. Combination of these two elements into one on-body device appears feasible and may even aid in detection of IIS failures. As AP technology becomes readily accessible, so too should development of combined IIS/CGM sensor devices which help to improve the success of this technology.

Author Disclosure

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