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COMMENTARY

Challenges in Delivering Smaller Doses of Insulin

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In this issue of *Diabetes Technology & Therapeutics*, Mianowska et al.[1] report a case series of three children under the age of 4 years with type 1 diabetes (T1D) whose blood glucose control was improved by the use of U10 (10 units/mL) diluted insulin in their insulin pumps. Although U100 insulin (100 units/mL) is today's standard concentration, both 40 units/mL and 80 units/mL were in common use prior to the introduction of U100 in 1973. The move to standardize insulin concentration worldwide was a major accomplishment, allowing the use of uniform, volumetric insulin syringes and reducing the incidence of dosing errors.[2] The one-size-fits-all approach to insulin concentration has not been without challenges, however. Severely insulin-resistant or obese patients often require large insulin doses. Aside from patient discomfort, such volumes could also affect the pharmacodynamics of some insulins. For these reasons, U500R (500 units/mL regular insulin) has continued to be available, and various new concentrated insulins have recently been developed: two new basal concentrated insulins, U200 (200 units/mL) insulin degludec and U300 (300 units/mL) insulin glargine as well as two bolus insulins, U200 (200 units/mL) insulin lispro and a derivative of insulin lispro at 500 units/mL (Fluorolog™; Thermalin Diabetes, LLC, Cleveland, OH). Additionally, there is a mixed-activity insulin under development, BIOD-531 (400 units/mL).[3] Of these new insulins, only the U300 insulin glargine (Toujeo®; Sanofi Aventis, Paris, France) is currently available in the United States and Europe, whereas U200 degludec (Tresiba; Novo Nordisk, Bagsvaerd, Denmark) is available in Europe only.

Meanwhile, individuals at the other end of the dosing spectrum—small children and infants—face their own set of dosing challenges with U100 insulin; however, there are currently no commercially available insulin products for human use that are more dilute than U100. The case series published in this issue[1] highlights some of the difficulties encountered by very young patients using U100 insulin therapy in insulin pumps. Here, expanding that conversation, we emphasize knowledge gaps, unmet dosing needs in young children, and barriers impeding progress.

Currently only about one in five pediatric patients in the United States meets the American Diabetes Association's recommended hemoglobin A1c (HbA1c) goal of <7.5%.[4] Management of T1D in very young children is especially difficult, as they are less able to communicate symptoms, have more erratic activity and eating patterns, and have limited insight into medical issues.[5] Young children are also more insulin sensitive, with lower total daily insulin needs per body weight.[6] Therefore, it is not surprising that children under 6 years of age are about 2.5 times more likely than older children to have hypoglycemic events.[7]

Beyond these considerations, shortcomings in the accuracy of syringes and insulin pen devices at small insulin doses have long been recognized.[8–10] Although there are no comprehensive data comparing accuracy of insulin delivery using currently available insulin syringes, pens, and pumps, a previous study has shown that insulin syringes, even those with ½-unit markings, are significantly less accurate and precise than pumps and pens at doses of 1 and 2 units.[11] The availability of insulin pens with half-unit increments has added some flexibility for younger children, but it does not address the minimum dose problem.[12,13] Because 0.5 units of U100 insulin may decrease the blood glucose of a typical 2 year old by 150 mg/dL (8.3 mmol/L),[6] even the smallest available insulin pen dose forces the user to tolerate blood glucose levels well above target range before being able to give a correction dose. For this reason, insulin pumps that allow mimimum doses and dose increments of 0.025–0.1 units have become an increasingly favored therapy for the youngest children, and outcomes studies have shown lowered risk of hypoglycemia with comparable or improved HbA1c levels and no increase of diabetic ketoacidosis risk in this age group.[14,15]

Despite pump manufacturers' claims to dose in increments as small as 0.025 units, the observations by Mianowska et al.[1] raise concern over how reliably very small basal and bolus doses are actually delivered to the patient in low flow situations. This case series describes three young children between 1 and 4 years of age treated by insulin pump. Despite prior insulin pump therapy and families being adherent to the recommended medical regimen, all three had suboptimal blood glucose control (mean HbA1c, 8.1%). After switching to diluted U10 insulin, HbA1c levels improved at 3 and 9 months (7.3% and 6.7%, respectively). Moreover, when two of the patients changed back to U100 insulin via pump, HbA1c values deteriorated to 8.5% and 8.7% within 2 months. Glucose variability also improved significantly as measured by blinded continuous glucose monitoring at baseline and 3 and 9 months of U10 therapy.

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Several possible mechanisms could have contributed to these patients' improved glucose variability. By design, the infused volume of U10 insulin is 10-fold higher and more in the typical functional range for the pump. It has also been speculated that a greater infusion volume may help overcome the pressure buildup at the tissue infusion site, allowing better delivery of infused dose.[16] Another factor is the finer increments in dosing allowed by diluted insulin. In this study, all three patients experienced problems with frequent air bubble accumulation within the pump tubing, which may have caused the unexplained hyperglycemic events. While using diluted insulin, the parents of these children noted an improvement in unexplained hyperglycemia and less frequent need to remove air from insulin pump tubing. Unfortunately, there is very limited literature regarding the incidence of these types of technical issues. Nonetheless, given the findings in this series, it can be speculated that increased volume from the use of a 10-fold dilution enabled improved insulin flow from pump to patient and thereby decreased the risk of air bubble obstruction. The results here are further supported by recent observations in a closed-loop study that showed that diluted insulin reduced glucose variability and risk of hypoglycmia in small children.[16]

In light of evidence that glycemic variability may be an additional contributor to long-term diabetes-related complications, diluted insulin may present additional benefits.[17,18] However, there are some important barriers to consider, particularly regarding the safety of such practice with current tools. As mentioned by Mianowska et al.,[1] only limited data exist regarding the pharmacologic stability of diluted insulin,[19] notwithstanding the prospect that a 1:10 dilution with on-the-market diluents would increase the exposure to metacresol, a possible human carcinogen, beyond the maximum allowable dose, and the use of normal saline for dilution has been reported but not rigorously studied. Furthermore, diluent is not carried by all pharmacies, few pharmacies will extemporaneously dilute insulin on-site, and there is no ''standard'' dilution agreed upon by the medical community. Even if the family is able to secure a reliable source of diluted insulin or is able to perform the dilution at home, there is the potential for miscommunication when communicating about dosing. This is a particular risk when the child is interfacing with the medical system and unintentional delivery of the ''wrong'' insulin to a child on diluted insulin could mean a potentially deadly overdose.

Aside from the safety concern, there is very little information about the pharmacokinetics and pharmacodynamics of diluted insulin. Of note is that differences in duration of action have been noted at the more concentrated end of the spectrum in U300 glargine[20] and U500R[21] insulin. It is encouraging to note that a recent study by Ruan et al.[22] compared U10 or U100 insulin administered by pump with overnight closed-loop delivery and showed no difference in pharmacokinetics. However, further study is warranted to understand the pharmacodynamics of diluted insulin in young children and whether varying dilutions behave significantly differently.

Despite the need for further information regarding the benefit of diluted insulin for young children and the potential role in both multiple daily injection and pump use, many roadblocks remain in answering whether diluted insulin would indeed be a better choice of therapy for young patients with very small insulin dose requirements. At our large tertiary referral center with over 3,600 individual patients seen in the pediatric clinic yearly, T1D patients under the age of 4 years make up only about 2.5% of the patient population, fewer than 100 patients, about the number of subjects needed to measure a half-point difference in HbA1c in a crossover trial. The case series of Mianowska et al.[1] points to a potential role for diluted insulin in improving glycemic variability or ease of use of insulin pumps, suggesting alternate outcome measures. Children with an early diagnosis of T1D accumulate a longer exposure risk, making optimal therapy strategies a pressing therapeutic need. Although the number of children under the age of 4 years with T1D is not large, epidemiologic evidence points to an increase in incidence of long-term complications in this age group. Large, multicenter studies are needed to better address how to care for this group of patients.

The agenda for future research should aim to better characterize the technical problems and accuracy of insulin pump infusion at small doses. We need further studies to establish the benefits of dilute insulin therapy and guide the community in the development of safe practices in spite of the abovementioned challenges. Finally, although the small number of patients limits the market incentive for pharmaceutical development, there is a potential for beneficial innovation in pump programming and insulin dilution options. The rising incidence of T1D, particularly among our youngest and most vulnerable patients, demands more action by the pharmaceutical industry and medical researchers to provide better therapeutic options that promote quality of life, safety, and optimal long-term outcomes.

Author Disclosure Statement

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