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SYMPOSIUM

Undeniable Need for Ultrafast-Acting Insulin: The Pediatric Perspective

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Abstract

Insulin therapy in youth with type 1 diabetes mellitus (T1DM) poses a special challenge because childhood is an unsteady state with increasing weight, height, and caloric needs, leading to varying insulin requirements. The current rapid-acting insulin analogs are not as fast and short-acting as needed to meet these challenges. This review describes the unique characteristics of insulin action in youth with T1DM based on previously published euglycemic clamp studies. It also explains the rationale behind the need for ultrafast-acting insulins to advance open- and closed-loop insulin therapy for the pediatric population with diabetes. Lastly, it briefly summarizes ongoing and future projects to accelerate insulin action in youth with T1DM.

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Introduction

During this year alone, 15,000 children will be diagnosed with type 1 diabetes mellitus (T1DM)[1] and will join millions of their peers who have already started their lifelong journey with insulin therapy. Almost all of these children will be on a rapid-acting insulin analog (RAI) and will all quickly learn the imperfections of insulin therapy. In fact, the insulin therapy in youth with T1DM poses a special challenge since childhood is an unsteady state with increasing weight, height, and caloric needs, which leads to varying insulin requirements. In addition, our current RAIs are neither as fast nor as short-acting as needed to meet these challenges. This review extends the elegant review of ultrafast-acting insulin (UFI) by doctors Heinemann and Muchmore[2] in this special issue of *Journal of Diabetes Science and Technology* with a focus on the rationale behind the need for UFIs in the pediatric population with diabetes.

Problems of Human Regular Insulin in Pediatrics

Insulin therapy, which was initially tested on a pediatric patient by Banting and colleagues, has come a long way since its invention in 1921. Compared to the early animal insulins, biosynthetic human regular insulin was purer and less painful to inject, but it still suffered from a number of pharmacological problems. The onset of action of regular insulin was delayed by up to 30 min after injection,[3] leading to the recommendation that patients inject it 30 min prior to meals. However, the unpredictable

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Abbreviations: (CL) closed-loop, (DCCT) Diabetes Control and Complications Trial, (PD) pharmacodynamics, (PK) pharmacokinetics, (RAI) rapid-acting insulin analog, (T1DM) type 1 diabetes mellitus, (UFI) ultrafast-acting insulin

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eating patterns of young children with T1DM made this recommendation impractical, inconvenient, and even unsafe to follow.

The pharmacokinetics (PK) and pharmacodynamics (PD) of human regular insulin were also a problem at the other end of the pediatric spectrum: treatment of adolescents with T1DM. Due to the peripheral resistance of puberty, very large premeal bolus doses of insulin are required in teenagers with T1DM to control 1- and 2-h postprandial glucose levels. However, with large premeal doses, the peak action of regular insulin is delayed to 3–4 h, and the duration of action is prolonged to 8 h or more. The delayed peak limits the ability to control postprandial hyperglycemia, and because puberty does not adversely affect hepatic sensitivity to insulin, the prolonged duration of action keeps the liver's production of glucose suppressed for many hours, which leads to late postprandial hypoglycemia.[4] These dose-related alterations in the time action profile of regular insulin explain, in part, why intensively treated adolescents in the Diabetes Control and Complications Trial (DCCT) had both higher hemoglobin A1c levels and a 50% increase in the rate of severe hypoglycemia compared to intensively treated adults.[5]

Advances in Insulin Therapy: Introduction of Rapid-Acting Insulin Analogs

A generation after the start of the DCCT, RAIs were introduced, and their faster action profiles, compared with regular insulin, offered the potential to more safely and effectively simulate normal plasma insulin profiles in patients with T1DM. Compared with regular insulin, increasing doses of RAI resulted in earlier and higher peaks and shorter duration of insulin action. Nevertheless, as more experience was gained in treating adult patients with T1DM with RAI, the shortcomings of these analogs became more apparent. The absorption rate of insulin was still not fast enough to eliminate postmeal hyperglycemia, and attempts to correct this by increasing the insulin dose still resulted in late postmeal hypoglycemia. Equally important for pediatricians, the PK and PD characteristics in children and adolescents had not been characterized.

In 2007, the pediatric T1DM research group at the Yale University School of Medicine sought to fill the gap in knowledge regarding time-action profiles of RAI by adapting the glucose clamp techniques for PK and PD studies in children and adolescents. Our first study examined the effect of puberty on standard 0.2 U/kg injections of RAI in 9 prepubertal and 12 pubertal patients with T1DM. While PK parameters were similar for both prepubertal and pubertal groups, the PD effects of insulin were significantly different.[6] Namely, the glucose infusion rates required to maintain euglycemia in the prepubertal subjects were approximately 37% higher than in the pubertal subjects due to the greater insulin sensitivity in the prepubertal subjects. One striking finding of this study was that the time to peak PD effect of insulin lagged 40 min behind the time to peak plasma insulin level (i.e., ~100 vs ~60 min) in both the prepubertal and pubertal subjects. In both prepubertal and pubertal subjects, the duration of action of the insulin bolus extended up to 4–5 h.

The next study examined the effect of type of RAI (i.e., lispro versus aspart) and age of the insulin infusion catheter site on PK/PD parameters in youth with T1DM on insulin pump therapy.[7] In this study, 17 adolescent subjects underwent euglycemic clamp studies on two separate occasions: once with a fresh insulin infusion catheter inserted 12 h prior to the study (day 1), and again with a catheter in use for approximately 84 continuous hours (day 4) after an identical 0.2 U/kg bolus of either lispro (n = 9 subjects) or aspart (n = 8 subjects).[7] An important observation from this study was that the PD responses to lispro and aspart were virtually identical both on day 1 and on day 4. While a small-scale study reported insulin infusion site adverse events on the third day of catheter use,[8] the age of the infusion catheter site had a significant accelerator effect on the PD profiles of both insulins in our study.[7] Compared to newer infusion sites (day 1), insulin PD responses using the older sites (day 4) were characterized by an earlier and greater peak insulin effect, as well as a shorter duration of insulin action.[7] These findings, recently termed "the Tamborlane effect" by Vaughn and colleagues[9], were replicated in an adult study investigating the effect of recombinant human hyaluronidase on insulin exposure and action 2 h and 74 h after insulin infusion site insertion.[9,10] While the cause for this effect was not determined, we speculated that increased blood flow and/or foreign body reaction might be playing a role. More recently, Clausen and colleagues[11] demonstrated such an increase in blood flow around the insulin infusion site from day 1 until day 4 in healthy adults. Techniques mimicking the changes in the aged infusion site to increase insulin absorption and action without adverse effects will be ideal options to generate a UFI profile.

Advances in long-acting insulin analogs introduced more flexibility in meal times and carbohydrate intake for

children with unpredictable appetite patterns. Due to the relatively flat time-action profiles of long-acting insulin analogs, children and adolescents with diabetes no longer have to eat lunch or a mandatory bedtime snack to cover for neutral protamine Hagedorn insulin's peak action. On the other hand, use of these "peakless" insulins puts a premium on compliance in taking multiple premeal bolus doses of rapid-acting insulin to cover the carbohydrate in each meal and large snack. In order to reduce the number of injections, a number of pediatric diabetes centers mixed RAIs with long-acting analogs, despite manufacturing companies' recommendations against doing so. While clinical use studies have failed to show a worsening in diabetes control with mixing rapid- and long-acting analogs,[12,13] most of the patients in these studies were not optimally controlled when the analogs were given either in separate or mixed injections. In two separate studies, we compared the PD of mixing lispro with glargine and aspart with detemir in adolescents with T1DM. In comparison to when the RAIs were given as separate injections, mixing the two types of insulin together just prior to injection markedly blunted and delayed the PD action of both RAIs.[14,15]

Rationale for Ultrafast-Acting Insulin

While earlier, sharper peaks and shorter duration of action of RAI are better than that of human regular insulin, persistent delays in absorption and the ≥5 h duration action of these analogs continue to contribute to the difficulties that are commonly seen in treating pediatric patients with T1DM. A clinical study undertaken in 56 pediatric patients with T1DM on pump therapy has shown postprandial glucose measurements by glucose sensor to be above 180 mg/dl 90% of time and above 300 mg/dl ~50% of the time during a 3-day study period, clearly demonstrating the limitations of RAI in controlling after-meal blood glucose.[16] More recently, data from the T1DM Exchange Clinic Registry in more than 10,000 youth with T1DM indicate that the mean HbA1c level of preteens being treated at leading pediatric diabetes centers in the United States is 8.3%, and this increases to 8.7% in teenagers.[17] While the rate of severe hypoglycemia has been reduced in children and adolescents with T1DM since the introduction of RAI and increased use of insulin pumps, severe hypoglycemia is still inexcusably high, and fear of hypoglycemia by patients and parents continues to be a barrier to optimal glycemic control,[18] fueling overcorrecting, overeating, and in some cases, excessive weight gain. Based on our clinical experience, teenagers with diabetes tend to overeat before exercise, and parents of our pediatric patients overfeed their young children before bedtime to prevent hypoglycemia during sleep. Another common practice is to overcorrect hypoglycemia with carbohydrate intake well above the recommended amount to prevent its recurrence. Some researchers have also postulated that hypoglycemia due to overshoot hyperinsulinemia, a prerequisite to overcome insulin resistance of puberty,[4,19] after the last meal of the day is the cause of dead-in-bed syndrome in adolescents with T1DM.[20,21] A UFI with a fast-in, fast-out profile will possibly reduce postprandial hyperglycemia and the frequency of hypoglycemia, easing the severe hypoglycemia anxiety for parents and patients. Consequently, there will be no need for overcorrecting and overeating for the pediatric population with T1DM who are clearly not immune to the obesity epidemic in the United States. Based on data from a national registry, 25% of pediatric patients newly diagnosed with T1DM are already overweight or obese.[22] The increase in mortality risk during treatment of diabetic ketoacidosis for obese youth with T1DM has been shown,[23] and the long-term effects of childhood obesity on long-term complications of T1DM are yet to be determined.

Ultrafast-acting insulins may have their greatest role in the future by enhancing the performance of closed-loop (CL) artificial pancreas systems. The first CL systems that will have application in the treatment of youth with T1DM will undoubtedly employ external sensors and pumps. While all technology for such external systems is already available, use of the subcutaneous route of insulin administration offers some challenges. As previously seen with human regular insulin in open-loop pump therapy, exaggerated postmeal hyperglycemic excursions and late postmeal hypoglycemia were observed in the initial CL studies[24] due to delayed and prolonged elevations in plasma insulin levels. These delayed plasma insulin responses were due to the nature of a reactive system that doesn't recognize the need for more insulin until after the subject has started eating and sensor glucose levels have started to rise. Moreover, unlike manual premeal bolus doses of insulin, which are infused over a few minutes with open-loop insulin pump therapy, meal-stimulated insulin delivery during CL control is stretched over more than 2 h. Late and prolonged increases in plasma insulin, in turn, result in a tendency for hypoglycemia before the next meal.[24]

In our first CL study, we demonstrated that the use of a "hybrid" CL system with administration of a manual "priming" insulin bolus by the patient 5–15 min before meals was able to reduce postprandial glucose excursions due to earlier increases in plasma insulin

levels.[25] Nevertheless, peak postprandial glucose levels still averaged ~200 mg/dl, and problems with overshoot hyperinsulinemia and late postprandial hypoglycemia were seen 6–7 h after the last meal, when the patients were sleeping at night. Thus, while the hybrid approach may reduce problems with hyperglycemia, it still did not completely normalize postprandial glucose levels. In addition, manual priming requires active involvement by the patient that defeats the purpose of a fully automated insulin delivery system.

Ultrafast-Acting Insulin Studies in Pediatrics

There are eight projects on the horizon for UFI that were reviewed in detail by doctors Heinemann and Muchmore[2]. So far, only the effect of the insulin infusion site-warming device on the acceleration of RAI absorption and action has been tested in the pediatric population. The preliminary results from the study revealed an acceleration of peak action by 35 min when insulin infusion site is warmed to 38.5 ^{0}C (101.3 ^{0}F) 15 min prior, and up to 90 min after a 0.2 U/kg bolus of insulin aspart is injected during a euglycemic clamp study.[26] There is ongoing work to test the effect of site warming at a higher temperature to accelerate insulin action even further and the potential to integrate this method to the CL system. Ultimately, the combination of different methods may be needed to confer a UFI profile that will approximate beta cell function closely enough to eliminate most of the problems with insulin replacement that have plagued clinicians for nearly a century.

Summary

There is obviously a critical need for faster-acting insulins both from the clinical and the research point of view to improve the treatment of diabetes, especially in children. Achieving faster, higher insulin concentrations and peak exposure will result in early glucose lowering effects and reduced postmeal hyperglycemia, which may lead to better glycemic control. The reduction in late postmeal exposure of insulin may lead to fewer hypoglycemic episodes, easing the tension on children and parents of children with diabetes who will be less tempted to overcorrect and snack. In addition, the desirable attributes of UFI profile will unlock one of the most important challenges on the path to CL systems and give momentum to research in this field.

The ultimate success in diabetes treatment lies in reproducing the physiologic pattern of insulin secretion and action from a healthy beta cell, therefore, the need for UFI is undeniable and will undoubtedly have a major impact on diabetes treatment directly and by related developments.

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