Hypoglycemia in Type 1 Diabetes

A still unresolved problem in the era of insulin analogs and pump therapy

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The Diabetes Control and Complications Trial demonstrated that in patients with type 1 diabetes, tight metabolic control achieved with intensive insulin therapy can reduce the risk of long-term microvascular complications. However, strict glycemic control carries an increased risk of severe hypoglycemia. Recurrent episodes of hypoglycemia, especially at young ages, can lead to hypoglycemia unawareness, exert adverse effects on neurocognitive function, and cause significant emotional morbidity in the child and parents. Although the introduction of the new insulin analogs in diabetes therapy and the use of continuous subcutaneous insulin infusion raised hopes for a solution to this problem, these modalities have not been associated with the expected reduction in hypoglycemic episodes. The findings suggest that the prevention of hypoglycemia in patients with type 1 diabetes lies in biologically controlled insulin secretion, as in islet transplantation, or the development of an autonomous closed-loop system that efficiently mimics the action of the pancreatic β-cells and maintains blood glucose levels within the desired range.

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The benefits of intensive management of type 1 diabetes were clearly established with the publication of the Diabetes Control and Complications Trial in 1993 (1). The Diabetes Control and Complications Trial demonstrated that tight metabolic control achieved with intensive insulin therapy is superior to conventional treatment in reducing the risk of long-term microvascular complications. However, strict glycemic control has been found to carry an increased risk of severe hypoglycemia (1), especially in patients receiving intensified insulin therapy (2). Nocturnal hypoglycemia, which accounts for about half of all severe episodes, is particularly dangerous because the warning symptoms are blunted or absent during sleep (3).

In healthy subjects with an intact counterregulatory defense mechanism, the presence of hypoglycemia generates autonomic symptoms that alert the individual. The body responds by suppressing insulin release and stimulating glucagon release from the pancreatic islet cells, thereby protecting the brain from glucose deprivation. By contrast, in patients with type 1 diabetes, the circulating insulin concentration depends on exogenous administration, so that an insulin suppression response is impossible. With time, the glucagon response, too, is diminished partly or entirely (4,5). Recurrent blunting of these autonomic processes, even over the short term (6), leads to hypoglycemia unawareness, which in turn further increases the risk of subsequent severe hypoglycemic episodes.

The risk of severe hypoglycemia appears to be higher in children and adolescents than in adults, with prevalence rates of up to 85.7 episodes per 100 patient-years (7). This is true as well for asymptomatic nocturnal hypoglycemia, with prevalence rates of 45–55% (8). Furthermore, hypoglycemic episodes in children are profound and prolonged (9) and may occur with any type of insulin treatment (10). The heightened risk in this age-group is at least partly attributable to the inability of children to recognize autonomic symptoms or (at younger ages) to relay these symptoms to their caregivers. In addition, although children and adolescents are encouraged to exercise regularly, exercise causes a profound metabolic disturbance and, when prolonged, can make plasma glucose concentrations difficult to manage. The natural tendency of children and adolescents for unpredicted eating and exercise exacerbates the danger (11).

Given the potentially adverse effects of recurrent hypoglycemia and the resulting hypoglycemia unawareness on neurocognitive function (12) and emotional well-being (of both child and parents), it continues to pose a serious hazard and a major obstacle to the achievement of tight glycemic control (13,14).

This review focuses on the reported experience with insulin analogs in diabetes therapy and the use of continuous subcutaneous insulin infusion (CSII) in terms of resolution of the problem of hypoglycemia.

HYPOGLYCEMIA AND INSULIN ANALOG THERAPY

— The term "insulin analog" describes insulin that has been bioengineered to modify its absorption or other properties (15). At present, three short-acting and two long-acting insulin analogs are available on the market. The short-acting insulin analogs, namely insulin aspart, insulin lispro, and apidra, were designed to better tailor insulin availability to physiological need. Small structural alterations in the insulin molecules reduce their tendency to self-associate into dimers and hexamers, thereby accelerating absorption. The properties of the molecule in relation to the insulin receptors remain unchanged. Insulin glargine, a long-acting analog, is a human insulin with amino acid alterations that make it more soluble at acidic pH and less soluble at physiologic pH. As a result, it precipitates locally in the tissue after subcutaneous injection, delaying its absorptions and prolonging its duration of action. In-

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Abbreviations: CSII, continuous subcutaneous insulin infusion.

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sulin detemir, another long-acting analog, is a fatty-acylated insulin engineered to bind to albumin in plasma, which delays its action after injection.

The more rapid pharmacodynamic effects of insulin lispro and insulin aspart make postabsorptive hypoglycemia less of a risk than with regular insulin (16). A large meta-analysis covering >1,400 patient-years reported a 25% reduction in the frequency of severe hypoglycemia with insulin lispro compared with regular insulin (17). A longer 1-year study of intensive treatment with neutral protamine Hagedorn (NPH) insulin and lispro versus human regular insulin at mealtime demonstrated fewer events of mild hypoglycemia (7.4 ± 0.5 vs. 11.5 ± 0.7 episodes/patient-month) in the study group, which in turn improved hypoglycemia awareness and counterregulation (18). By contrast, in a 3-year study of insulin lispro compared with the previous regimen with regular insulin in 44 children and adolescents, Garcia et al. (19) found no change in metabolic control and no difference in the number of patients with severe hypoglycemic events.

The risk of nocturnal hypoglycemia rises in young children receiving evening injections. Given that the administration of a small dose of short-acting insulin analog before the evening meal helps to control blood glucose levels during the late evening and early part of the night, Mohn et al. (20), in a double-blind crossover study of 14 adolescents, examined the benefit of administering insulin lispro compared with human insulin after the bedtime snack. The lispro group showed a pronounced rise in glucose level, and their blood glucose concentration then remained higher than with human insulin until 3:00 A.M. and had an overall reduction in nocturnal hypoglycemia (20).

In a study of the role of physical exercise, the risk of hypoglycemia was found to be increased when the exercise followed too soon after short-acting insulin analog administration (21).

Fewer studies have been conducted on the long-acting insulin analogs. In adults, basal-bolus treatment with insulin glargine or insulin detemir led to similar glycemic control as NPH insulin, but with a flatter pharmacokinetic profile and lower risk of hypoglycemia (22,23). Similar findings were noted in a study of 349 children and adolescents, in whom insulin glargine was associated with less severe hypoglycemia than NPH insulin but no difference in glycosylated hemoglobin levels (24), and in a study of 114 children given insulin glargine at bedtime and NPH insulin in the morning (25). However, Colino et al. (26) reported that although the rate of severe hypoglycemia decreased with insulin glargine therapy in the pediatric age-group, the difference from NPH insulin did not reach statistical significance.

Together, these findings indicate that the use of insulin analogs in patients with type 1 diabetes is associated with a tendency toward a reduced frequency of hypoglycemia.

HYPOGLYCEMIA AND INSULIN PUMP THERAPY —

Considering the variations in insulin absorption and serum insulin profiles during long-acting insulin use, we would expect CSII to be a very useful tool for the prevention of hypoglycemia. However, there has been little solid evidence to date to support this assumption. Although randomized controlled trials conducted in adults demonstrated a significant decrease in the rate of severe hypoglycemia with CSII (27), in children, the findings were highly variable. Several observational pediatric trials reported a decrease in the rate of severe hypoglycemia with CSII, concomitant with a reduction in glycosylated hemoglobin levels (28–32), but none of the randomized controlled trials (33–38) showed a significant difference in the frequency of severe hypoglycemia between CSII and multiple daily injections. Weintrob et al. (33), in a crossover study of schoolchildren randomized into CSII and multiple daily injection arms, noted no difference in symptomatic hypoglycemia. However, there was one episode of severe hypoglycemia in the CSII group as opposed to three in the multiple daily injection group. Fox et al. (37) found that subjects using CSII had more mild/moderate fasting and predinner hypoglycemia. However, this study was not powered to specifically detect differences in hypoglycemia.

In patients using CSII, the frequency of nocturnal hypoglycemia increased after prolonged physical exercise (39). The DirecNet study group showed that the risk of hypoglycemia with exercise can be markedly reduced with CSII by suspending the basal insulin infusion during exercise (40).

Pump therapy itself can cause hypoglycemia if inappropriate extra doses of insulin are administered (41). However, although pump malfunction was an early concern, the current generation of pumps contains a memory of insulin administration with a lockout safety feature that prevents overdose.

These findings indicate that in some diabetic patients, the frequency and severity of hypoglycemia can be reduced with CSII treatment. Continuous glucose monitoring will undoubtedly improve that ability of patients to monitor for hypoglycemia, and future studies will allow us to better characterize this risk in young patients.

SUMMARY AND FUTURE GOALS —

In conclusion, insulin analogs or CSII allow patients greater flexibility in the timing of meals and exercise, thereby enhancing their quality of life. Nevertheless, current insulin replacement regimens are far from perfect, and they do not replicate normal insulin secretion. Only a slight clinical benefit in terms of hypoglycemic events has been observed in most studies on pediatric and adult populations. The ideal solution is an autonomous closed-loop system that maintains blood glucose levels within the desired range and prevents severe hypoglycemia, while eliminating the necessity for decision-making by the patient or parents. The development of such an "artificial pancreas" requires the availability of three key interconnected elements: a safe insulin delivery device (insulin pump) that stores and releases insulin reliably and accurately; an accurate biocompatible glucose-sensing unit capable of frequent or continuous sampling; and a control system that modulates the delivery of insulin, glucose, glucagon, or amylin according to blood glucose levels (42). We look forward to the new technological advancements that will improve insulin replacement therapy and make these goals possible.

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