Nighttime Continuous Subcutaneous Insulin Infusion Revisited

A strategy for improving insulin delivery

It has been 20 years since the demonstration that intensive insulin therapy (IIT) can result in near-normoglycemic levels (1-4). Despite this evidence, IIT has been used infrequently in children and adolescents. The majority of the early studies of type 1 diabetic children and adolescents used continuous subcutaneous insulin infusion (CSII) as the mode of therapy (5-10). It has also been shown that, in adolescents, a regimen of premeal regular insulin plus NPH at bedtime was almost as effective as CSII (11,12). Another strategy that combined nighttime CSII with daytime multiple daily insulin injections (MDI) was also shown to be as successful as CSII or MDI alone in achieving near normal HbA1c levels (13). Despite these encouraging results, widespread efforts to improve blood glucose control were put on hold for a number of years, because clinicians and patients were awaiting the results of the Diabetes Control and Complications Trial (DCCT). In 1993, the DCCT group published its first manuscript, which showed that IIT with MDI and/or CSII was much more effective than conventional therapy (CT) in decreasing HbA1c levels (14). Even though near normoglycemia could not be maintained over prolonged periods of time with either method, the improvement of HbA1c levels observed during the 7.4 years of the trial was good enough to substantially reduce the risk of progression of diabetic microangiopathy. These results, combined with the availability of smaller more reliable insulin pumps, insulin pens, and infusion sets, encouraged diabetologists around the world to renew their efforts to use MDI and CSII in a larger number of patients of all ages (15-17).

In this issue, Kaufman et al. (18) report the results of a randomized crossover trial that compared the use of nighttime insulin pump therapy beginning at dinner (nighttime CSII) combined with a mixture of NPH plus lispro before breakfast with a regimen of 3 injections/day in a group of 10 children <10 years of age with a history of nighttime hypo- or hyperglycemia. Nighttime CSII resulted in significantly lower mean average, breakfast, and bedtime blood glucose levels; lower mean fructosamine levels; and an increase in the percentage of blood glucose values within the target range of 70-150 mg/dl. This is an important study for pediatric diabetologists. There have been very few reports on the feasibility of administering CSII to children (7,10). In particular, this is the first study that has used nighttime CSII only in children. Nighttime CSII combined with daytime MDI was first implemented 20 years ago in adolescents and young adults for up to 10 months of therapy (13). This strategy was devised when it was noted that individual fasting blood glucose values were more variable with MDI than with CSII (12). Recently, it has been shown that, in young adults, nighttime CSII can improve counterregulatory responses and warning symptoms in patients with hypoglycemia unawareness (19). Kaufman et al. concluded that the nighttime CSII group had less hypoglycemia, although this conclusion is not very evident given the data shown. Because the study was very short, it remains to be seen if nighttime CSII is clearly superior to thrice-daily injections over the long term. It is difficult to exclude the possibility that increased parental involvement and adherence led to the improvement of blood glucose control in the nighttime CSII group; parental concerns about their children’s safety may have been heightened by the use of a new treatment. One wonders if increased familiarity with the pump over time could lead to lapses in supervision. A mechanical problem that goes unnoticed could result in severe hyperglycemia, because the use of lispro provides shorter insulin coverage than the use of regular insulin. In fact, ketoacidosis was a fairly frequent complication reported in the early studies of young patients, even when regular insulin was used. In the DCCT, adolescent and adult subjects on CSII had significantly lower HbA1c values than subjects on MDI (6.8 vs. 7%), and they also had slightly higher frequencies of diabetic ketoacidosis and hypoglycemia with coma or seizure than subjects on MDI (20). A recent report of a 2-year prospective study of children and adolescents aged 1-18 years who were treated with MDI (21) showed levels of HbA1c comparable with those of the adolescents in the DCCT and with those of the children in Kaufman et al.’s study; however, these patients showed lower frequencies of hypoglycemia (1.17-1.43 events/patient-year) than those of patients observed in the DCCT. Although it is difficult to extrapolate what the long-term frequency of hypoglycemia would have been in Kaufman et al.’s study, the results show the potential of nighttime CSII to improve blood glucose control and to, perhaps, reduce the frequency of nocturnal hypoglycemia in children, a complication that has been shown to be associated with abnormal counterregulation (22) and possibly with an increased risk of memory impairment (23). The data obtained by Kanc et al. (19) from a study of adult patients who used nighttime CSII are very encouraging, and there are no obvious reasons why this form of therapy will not be as effective in young children.

Several prospective studies have shown that, in children and adolescents, severe hypoglycemia is a very frequent event with both CT and IIT; ~50% of the total daily events occur nocturnally (24,25). During sleep, the autonomic symptoms may not always wake the patient, and unrecognized nocturnal hypoglycemia may result in hypoglycemia unawareness, which would predispose the patient to hypoglycemia during the day (26). Excessive counterregulation, if present, and/or food intake may result in hyperglycemia, which may induce overinsulinization and further hypoglycemia. The incidence of nocturnal hyperglycemia during nighttime CSII could be decreased, as previously demonstrated in a study on 20 patients on CSII (27). Patients were randomized to receive their usual bedtime snack or to receive extra food 1.5 h
after the bedtime snack if blood glucose levels were <120 mg/dl. Results showed that the probability of nighttime hypoglycemia and morning hyperglycemia could be minimized to 20% at bedtime blood glucose values of ~140 mg/dl. Because there is currently no clear evidence of the long-term effects of hypoglycemia on the cognitive function of young children, avoidance of hypoglycemia in this age-group is paramount. In addition to the potential risk of cognitive impairment, severe hypoglycemia may induce adverse psychological reactions in patients and caretakers. A common response to such reactions is to maintain high blood glucose levels, particularly at bedtime. Thus, repeated episodes of hypoglycemia may induce poor blood glucose control for long periods of time.

Nighttime CSII has several advantages. It provides the delivery of insulin with more physiological pharmacokinetics. It results in a square-wave insulin profile (28), avoiding the peak and waning effect of NPH that causes large blood glucose nadirs in the middle of the night and hyperglycemia in the early morning. With CSII, the infusion rate can be adjusted according to the patient’s requirements. In young patients, nighttime CSII offers a flexible lifestyle because the pump can be connected before or after dinner, depending on the child’s activities, and thereby avoids the inconvenience of carrying the pump during the day. During holidays and sleep-overs, nighttime CSII can be replaced by NPH. The disadvantages of nighttime CSII include the time spent in the preparation and the technical skills required to safely handle the infusion and costs incurred by families, which, for uninsured patients, could be prohibitive. It remains to be seen if the use of lispro insulin will not result in an increased ketosis or ketoacidosis in the case of pump malfunction.

Nighttime CSII in children is a simple strategy that can improve glycemic control as long as it is administered under careful parental supervision. However, it should be emphasized that the success of diabetes therapy in this population does not depend only on the number of insulin injections, the use of CSII, the frequency of blood glucose monitoring, or the access to a diabetes specialist. Both the presence of a stable family environment that is capable of providing support to the patient and access to a specialized multidisciplinary health care team that is available for guidance, education, and maintaining motivation also play a role in determining the outcome of diabetes treatment.

Alicia Schiffrin, MD

From the Department of Medicine and Pediatrics, McGill University, and the Division of Endocrinology, Jewish General Hospital, Montreal, Quebec, Canada.

Address correspondence to Alicia Schiffrin, MD, Division of Endocrinology, E-104, Jewish General Hospital, 3755 Cote Ste. Catherine Rd., Montreal, PQ, H3T 1 E2 Canada. E-mail: aschiff@end.jgh.mcgill.ca.

References


