Premeal Insulin Treatment During Basal-Bolus Regimen in Young Children With Type 1 Diabetes

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The introduction of insulin analogs in clinical practice suggests updating therapeutic schemes in subjects with type 1 diabetes. We read with interest the recent article by Alemzadeh et al. (1), which was designed to determine the feasibility of a flexible multiple daily insulin regimen in preschool children. Rapid-acting insulin analogs offer unquestionable advantages due to their pharmacokinetics and pharmacodynamic properties. However, when used in a basal-bolus regimen, they also need great accuracy in determining the carbohydrate content of the meal. A small mistake could generate a significant problem, including hyperglycemia or hypoglycemia. The meal carbohydrate count system seems to be effective and safe in controlling postmeal hyperglycemia in children treated with continuous subcutaneous insulin infusion (2), but when rapid-acting analogs are associated with glargine at bedtime, they could leave a "window" of low plasma insulin levels during the first portion of the night. Indeed, glargine-insulin plasma levels could not yet be consistently stable (3).

Moreover, when using rapid-acting insulin analogs, children need an additional insulin shot to control the carbohydrate intake of their afternoon snack, which is a common practice among children living in the Mediterranean area. The object of the present study was to evaluate fasting and postmeal metabolic effects in prepuberal children treated with glargine and regular or rapid-acting insulin using the carbohydrate counting system.

RESEARCH DESIGN AND METHODS

— We recruited 30 prepuberal children aged 8.1 ± 1.8 years (means ± SD) with type 1 diabetes, having basal C-peptide <0.1 nmol/l, diabetes duration 5.2 ± 2.0 years, HbA_{1c} (A1C) 7.5 ± 1.1%, and BMI 18.0 ± 2.8 kg/m^2, who were without other autoimmune diseases, treated with multiple daily insulin injections, and using NHP and regular or rapid-acting insulin. Informed consent was obtained from parents before the study. All children were shifted from NPH to glargine insulin administered at dinnertime (8:00 P.M.) and randomized into two groups: A, receiving regular recombinant human insulin 30 min before each meal (breakfast, lunch, and supper) and B, rapid-acting insulin analog (aspart insulin) 2 min before meals.

Children in group B received an additional insulin shot before the afternoon snack. All parents were instructed on carbohydrate counting and received a personalized diet, including four menus with the same carbohydrate contents for each meal. The starting insulin/carbohydrate ratio was defined for each patient based on a weekly food diary prepared before the study. Children and parents used a personal blood glucose meter (OneTouch Ultra; LifeScan) and a diary to note glycemia and food consumption. During the 18-week study period, parents were asked to perform five blood glucose tests everyday on their children: fasting (6:00–9:00 P.M.), before meal (breakfast, lunch, afternoon snack, and supper), and at bedtime (11:00 P.M.). Twice a week, self-blood glucose monitoring was also requested at 2:00 A.M. and at 10:00 A.M. An afternoon seven-point blood glucose profile was performed at inclusion and after 12 weeks of treatment for both groups in hospital setting. During the 2-week visit, we verified all children were following the protocol, including subjects taking regular insulin 30 min before meals, and continued to do so during the study as evidenced by diary entries. A blood glucose level <70 mg/dl was defined as hypoglycemia, while the presence of seizures or a clinical condition in which the child is unconscious was defined as severe hypoglycemia. Parents were instructed to adjust the insulin dose based on their diary. Institutional board approval was obtained for this study.

Changes in percent A1C (primary end point) were analyzed using repeated-measures ANCOVA. Data are expressed as means ± SD and were considered to be significantly different at $P < 0.05$.

RESULTS

— Mean daily blood glucose and daily glucose variability, expressed as SD, decreased from baseline similarly in both groups ($P > 0.237$, data not shown). However, fasting glucose levels from home glucose monitoring decreased more in group A than in group B ($P = 0.012$) (Fig. 1), and A1C decreased in group A (from 7.5 ± 0.8 to 7.0 ± 0.4%) but not in group B (from 7.5 ± 1.4 to 7.4 ± 0.5%) ($P = 0.018$). The mean afternoon blood glucose at baseline was higher in group A than in group B, whereas they were similar by the end of the study (165 ± 49 vs. 160 ± 52 mg/dl, group A vs. B, respectively; $P = 0.113$); 2-h postprandial blood glucose values were also similar (143 ± 19 vs. 133 ± 18, group A vs. B, respectively; $P = 0.175$). Hypoglycemic episodes with blood glucose values <70 mg/dl were similar in groups A and B (0.214 and 0.18 episodes · patient^{-1} ·

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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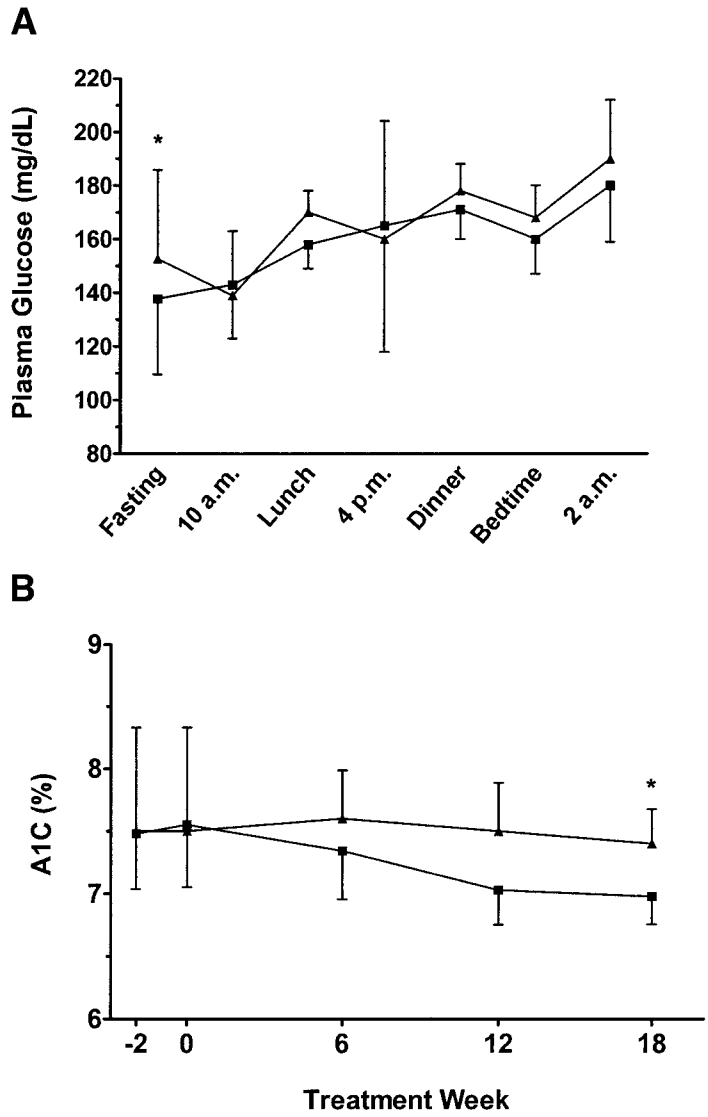

Figure 1—A: *Data on capillary blood glucose collected at the end of the study (based on self-monitoring) in the two groups of type 1 diabetic children receiving regular recombinant human insulin (group A,* ■*) or rapid-acting insulin analog (group B,* ▲*).* B: *Changes in A1C over time in group A (*■*) and group B (*▲*). Data are means ± SD.* *P $<$ *0.05 with between-group test.*

day^{-1}, respectively; $P = 0.117$), as were those with blood glucose <50 mg/dl (0.045 and 0.035 episodes · patient^{-1} · day^{-1}; $P = 0.209$).

CONCLUSIONS — To our knowledge, this is the first report focusing on premeal insulin treatment in prepuberal children using the carbohydrate counting system and designed to investigate this issue in "real life." Consistent with other clinical trials, comparing glargine with NPH insulin (4,5), our randomized study has shown a reduction of fasting blood glucose in both groups; however, the effect was significant only in children receiving regular insulin. We could speculate that this result depends on the higher insulin plasma levels during the first hours of the night, blunting a late postprandial rise of blood glucose. The afternoon blood glucose profile is influenced by the usual snack of the children and the reduction of glargine insulin action after 20 h from the injection. Interestingly, in the present study, we could obtain a similar presupper blood glucose value in the group treated with regular insulin in which the presnack insulin shot was not used. Moreover, a significant change of A1C was seen in children treated with regular insulin, suggesting that this insulin can assure better plasma levels between meals. On the other hand, Raskin et al. (6) suggested that the failure to produce improvement of A1C in patients receiving lispro insulin could be due to higher glucose levels at other times of the day (6).

Glargine insulin was very helpful in minimizing nocturnal hypoglycemia in this group of school children, without differences between regular or rapid-acting insulin. Insulin analogs seem to permit a more flexible lifestyle; regular insulin with an individualized training of carbohydrate counting seems to allow the same good control without the afternoon shot. Meal insulin treatment remains an open question. Clinical management suggests that education is the best route to obtaining good postmeal glycemic control. Further well-defined studies will provide more information to enable achieving the best metabolic control for each child with type 1 diabetes.

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