Reducing postprandial hyperglycemia with adjuvant premeal pramlintide and postmeal insulin in children with type 1 diabetes mellitus


Objective: The purpose of this study was to determine the effect of adjuvant premeal pramlintide with postmeal insulin on postprandial hyperglycemia in children with type 1 diabetes mellitus (T1DM).

Methods: Eight adolescents with T1DM on intensive insulin therapy participated in an open-label, non-randomized, crossover study, comparing postprandial glucose excursions in study A (prescribed insulin regimen and given premeal) vs. study B (pramlintide + insulin). Prandial insulin dose for study B was decreased by 20% and given postmeal, while pramlintide was given just before the meal. Blood glucose (BG), glucagon, and pramlintide concentrations were measured basally and at timed intervals during a 300-min study period.

Results: Postprandial incremental BG for the duration of the study was reduced in study B vs. study A with AUC(2-60 to 300 min) (area under the curve) at 6600 ± 2371 vs. 20 230 ± 3126 mg/dL/min (367 ± 132 vs. 1124 ± 174 mmol/L/min) (p < 0.001). Glucagon concentration was suppressed for ~120 min following administration of 30 μg of pramlintide and postmeal insulin (p < 0.003). No severe hypoglycemic episodes were experienced in this study.

Conclusions: Postprandial hyperglycemia is considerably reduced in adolescents with T1DM when treated with fixed-dose premeal pramlintide, and precisely calculated postmeal insulin, without significant side effects.

In type 1 diabetes mellitus (T1DM), insulin and amylin deficiencies occur secondary to the autoimmune destruction of pancreatic β-cells (1, 2). Insulin monotherapy aimed at mimicking physiologic insulin secretion with basal–bolus regimen (3, 4) fails to achieve euglycemia (2). Postprandial hyperglycemia occurs (5, 6) despite an increase in premeal insulin boluses by 60% (7). Although the function of basal amylin concentrations is yet to be established, amylin replacement with pramlintide alongside insulin therapy effectively decreases immediate postprandial glucose concentration (8, 9).

Amylin, a neuroendocrine hormone secreted in concert with insulin by the pancreatic islet β-cells and under feedback control by insulin (10, 11), is secreted in response to increased plasma glucose concentration (12) and/or a nutrient stimulus (12, 13). Amylin secretion is minimal or absent in patients with T1DM (2), whereas in those with type 2 diabetes mellitus, amylin concentrations progressively decrease with increasing destruction of pancreatic β-cells (2, 14). Amylin presumably suppresses hepatic glucose production by inhibiting postprandial glucagon secretion (15, 16). Amylin also delays gastric emptying, thereby retarding rate of nutrient delivery to the small intestine, resulting in the decreased rate of intestinal carbohydrate absorption and lowered postprandial glucose concentrations (2, 17).
Pramlintide is a synthetic, equipotent analog of amylin (9) and has a $C_{\text{max}}$ of 20 min and a $t_{1/2}$ of 48 min (18). Adjunctive therapy with pramlintide in T1DM results in the reduction of postprandial hyperglycemia by mechanisms identical to that of amylin (17, 19–21). When given in combination with insulin, hypoglycemia may result unless the dose of insulin is reduced (22). Hypoglycemia related to pramlintide may occur because of the simultaneous effects of delayed gastric emptying and peaking of the rapid-acting insulin analog. Hence, delaying the delivery of prandial insulin may decrease the incidence of postprandial hypoglycemia. However, literature search did not yield any studies that examined whether pramlintide could be given before and insulin after the meal. In this study, we hypothesized that pramlintide given before a meal and insulin given 15 min after starting on a meal would be more effective in reducing postmeal hyperglycemia than insulin delivery before meal without adjuvant pramlintide and reduce postprandial hypoglycemia associated with concurrent pramlintide dose.

Methods

Following approval by the Institutional Review Board at Baylor College of Medicine, eight adolescents (six males, two females) with T1DM were recruited to the open-labeled, non-randomized, crossover study. Two male subjects were African American; the remaining subjects were all Caucasian. Six subjects were on insulin pump therapy and the two on insulin glargine self-administered the drug at ~90 min. Subjects were diagnosed with T1DM at least 1 year earlier, had hemoglobin A1c of $<8.5\%$, and were either receiving insulin glargine and a rapid-acting insulin analog or on insulin pump therapy. Subjects had their last meal before 12 midnight and stayed at our research center from 07:00 hours until completion of the study at 14:00 hours. Study A was performed before study B.

Basal insulin doses of the subjects were kept constant through studies A and B. No subject was prescribed pramlintide any time in the past before participation in this study.

Study A

Insulin therapy was continued as per prescribed home regimen without pramlintide. Subjects self-administered a rapid-acting insulin analog (aspart or lispro) bolus based on their individual insulin: carbohydrate ratio, following which they received 591 ml of Boost High Protein Drink (360 calories, 50 g carbohydrate, and 12 g fat) at 09:00 hours (0 min). The Boost was consumed in 5–7 min. Blood samples were collected for the analysis of blood glucose (BG) levels at 0, −10, and 0 min and every 10 min thereafter for the first hour, every 20 min for the second hour, and every 30 min until the study ended. Blood samples were also collected throughout the study at multiple time points for the analysis of insulin and glucagon levels. Subjects were provided with lunch at 14:00 hours and discharged.

Study B

The study protocol was identical to study A except 30 μg of pramlintide was administered subcutaneously immediately before drinking the Boost at 09:00 hours, and no insulin was given before the meal but was given 15 min after the meal (09:15 hours) and the dose was reduced by 20%. Study B was conducted within 3–4 wk of study A.

BG concentrations were measured using a glucose analyzer (2300 Stat Plus; Yellow Springs Instruments, Yellow Springs, OH, USA).

Glucagon and pramlintide assays were conducted by Tandem Labs, West Trenton, NJ, USA. Glucagon was measured by radioimmunoassay using an antibody specific to pancreatic glucagon. Blood samples were analyzed for pramlintide acetate using immunoradiometric assay (23).

Statistical analysis

Baseline descriptive statistics were obtained with the advanced model of SPSS version 13.0 (SPSS Inc, Chicago, IL, USA). Pharmacokinetic (PK) properties of pramlintide were obtained using the software PK SOLUTIONS 2.0 (Summit Research Services, Montrose, CO, USA). Comparative statistics, figures, and graphs were generated using GraphPad PRISM version 4.03 (GraphPad Software Inc, San Diego, CA, USA). Mean area under the curve (AUC) was compared using two-way ANOVA for repeated measures. Data, unless otherwise stated, were presented as mean ± SD and were considered significant at $p \leq 0.05$.

Results

All eight subjects completed both studies A and B with no adverse events. Their baseline characteristics are shown in Table 1.

Blood glucose

Glucose excursions were significantly reduced in study B (Fig. 1A, B). The total AUC$_{(-60 \text{ to } 300 \text{ min})}$ ± SEM decreased ($p < 0.001$) in study B vs. study A: 6600 ± 2371 vs. 20 230 ± 3126 mg/dL/min (367 ± 132 vs. 1124 ± 174 mmol/L/min). Although the rise in BG in study B was gradual and had a lower peak, it continued to rise until 240 min after which it paralleled that of study A. Mean AUC$_{0 \text{ to } 240 \text{ min}}$ in study B vs. study A was 3698 ± 2080 vs. 17 870 ± 2535 mg/dL/min (205 ± 116 vs. 993 ± 141 mmol/L/min) ($p < 0.0006$).
Glucagon

Pramlintide reduced (p < 0.003) the secretion of glucagon for ~120 min following its administration (Fig. 2A, B). Mean AUC(0 to 120 min) ± SEM of study B vs. study A was 6060 ± 459 vs. 7575 ± 479 mg/mL/min (6060 ± 459 vs. 7575 ± 479 ng/L/min). After 120 min, glucagon levels trended higher in study B than in study A, but the differences were not statistically significant.

Pramlintide

Mean pramlintide excursion during study B is shown in Fig. 3. PK properties of pramlintide are presented in Table 2.

Nausea/vomiting

Nausea was experienced with the introduction of pramlintide in only one study subject, and no vomiting was noted.

Hypoglycemia

No episode of severe hypoglycemia was experienced by any of our subjects.

Discussion

Current insulin therapy requires that insulin be taken before meals. The dose calculation is dependent on the estimated grams of carbohydrate that patients think they will consume. Even if they feel satiated, they will still have to eat the intended amount of carbohydrates for fear of hypoglycemia later. However, they will have to take another insulin injection if they want to eat more than they initially estimated. This predicament could be resolved if they were able to take their exactly calculated insulin dose after a meal. In addition, patients with diabetes continue to have marked postprandial hyperglycemia even with accurate carbohydrate count and exact insulin dose.

In the current study, we showed that adjunctive pramlintide therapy given before meal and insulin given after meal were effective in reducing postprandial hyperglycemia. Moreover, the reduction in glycemic excursions occurred with a 20% reduction in insulin dose when pramlintide was administered. It also allowed patients with diabetes to eat carbohydrates and then calculate insulin dosing based on the carbohydrate amount they actually ate rather than on the presumed amount to be eaten and avoided potentially inaccurate premeal dosing. Our study, with fixed dose of 30 µg pramlintide taken just before meal and bolus insulin reduced by 20% and delayed until 15 min after the meal, yielded a statistically significant reduction in postprandial glucose levels comparable to the results obtained when pramlintide and insulin were administered before meals (24, 25). These results were seen despite weaknesses in our design, namely the absence of an arm studying the premeal administration of both pramlintide and bolus insulin, and the inability to tease the effect of a lowered and delayed dose of bolus insulin in study B from the effect of pramlintide as timing and dose of bolus insulin differed in study A.

The drawback in implementing an after-meal insulin injection will be the extent of compliance of those pediatric patients not on the pump who would need to remember when to take their bolus injections. However, for those on the pump, preprogrammed postmeal insulin boluses would be a very accurate method of insulin delivery. The limitation of our study was in the use of a standardized mixed liquid meal. In real life,
both solid and liquid meals are consumed. To address these limitations, projects are in progress that address postmeal insulin timing, basal adjustments, and mixed meals as well as those that will arise from a child’s hesitation in increasing the number of injections and tolerating nausea.

Pramlintide, a relatively new amylin agonist, is effective as adjunctive therapy to intensive insulin management with statistically significant reduction in postprandial glucose excursions (26), without increasing the risk of episodes of severe hypoglycemia (9, 25). The postprandial glucose surge observed soon after a meal is curbed significantly with pramlintide (27). Maggs et al. reported that plasma glucose concentrations did not rise for the first hour after the meal, increased gradually during the next 2 h, then slowly decreased toward baseline with either mealtime pramlintide or at −15 min (26). By delaying bolus insulin to 15 min after meal, we found that plasma glucose did not increase for the first 90 min postmeal. In fact, BG trended lower during this period. It is possible that these differences in glycemic excursions between the adult and our pediatric population be attributed to a higher Cmax and a shorter Tmax and elimination t1/2 in adults (2, 18, 28).

In conclusion, pramlintide, an amylin agonist, can be used premeal with postmeal insulin dosing in adolescents with T1DM. This regimen may improve postprandial glycemia and allow flexibility in carbohydrate intake.

Acknowledgement
This investigator-initiated trial was supported by Amylin Pharmaceuticals, Inc.

References
3. RENARD E. Intensive insulin therapy today: 'basal-bolus' using multiple daily injections or CSII? Diabetes Metab 2005: 31: 4S40–4S44.
6. KAUFMAN FR, GIBSON LC, HALVORSON M, CARPENTER S, FISHER LK, PITUKWICHWANONT P. A pilot study of the continuous glucose monitoring system: clinical decisions


