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Original Article

Insulin glargine improves hemoglobin A1c in children and adolescents with poorly controlled type 1 diabetes

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Abstract: The pediatric diabetes team at the University of Minnesota made a clinical decision to switch patients with type 1 diabetes with a hemoglobin A1c level greater than 8.0% to insulin glargine in an effort to improve glycemic control. Retrospective chart analysis was performed on 37 patients 6 months after the switch to insulin glargine therapy.
Results: After 6 months, the average hemoglobin A1c level in the entire cohort dropped from 10.1 ± 2.0 to $8.9 \pm 1.6\%$ ($p = 0.001$). Thirty patients responded with an average hemoglobin A1c drop of $1.7 \pm 1.5\%$, from 10.3 ± 2.2 to $8.6 \pm 1.5\%$ ($p < 0.001$). Seven patients did not respond to insulin glargine therapy, with an average hemoglobin A1c rise of $1.0 \pm 0.8\%$ from a baseline of $9.5 \pm 1.0\%$ to $10.4 \pm 1.4\%$ ($p = 0.01$). The greatest response was seen in children with an A1c > 12.0%, who dropped their hemoglobin A1c by $3.5 \pm 1.9\%$. Compared with responders, non-responders had significantly less contact with the diabetes team in the form of clinic visits and telephone conversations both before and after initiation of glargine therapy. Sixty-two per cent of patients received insulin glargine at lunchtime, when injections could be supervised at school. Three episodes of severe hypoglycemia occurred after initiation of insulin glargine therapy.
Conclusions: Insulin glargine substantially improved glycemic control in children and adolescents with poorly controlled type 1 diabetes. This response was most remarkable in those with a baseline hemoglobin A1c level > 12.0%, and may have been related to increased supervision of injections.

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The Diabetes Control and Complications Trial (DCCT) unequivocally showed the close relation between the degree of metabolic control and diabetes microvascular complications (1). This was true in adolescents as well as adults. Although retinopathy and nephropathy are rare in prepubertal children with type 1 diabetes, they show an increasing prevalence during the pubertal and early postpubertal years (2–4), and evidence suggests that the years prior to puberty contribute to the risk of microvascular injury (3, 5, 6). For any given duration of diabetes after puberty, the prevalence of retinopathy is significantly greater in those patients diagnosed with diabetes before puberty compared with those diagnosed in the pubertal period (3, 6), and prepubertal diabetes duration is related to the presence of retinopathy in adolescents (7). Early increases in albumin excretion within the normal range can be detected in children and adolescents with type 1 diabetes and predict subsequent development of microalbuminuria (8). Sustained hyperglycemia is related to progression of microalbuminuria in adolescents, and improved metabolic control may normalize microalbuminuria (4).

Whereas the evidence that good metabolic control should be sought in pediatric diabetes patients is clear, effective treatment of this population is a challenge. Despite significant effort by the health care team, hemoglobin A1c levels were higher in adolescents than in adults in the intensive control arm of the DCCT (8.06 vs. 7.12%) (1). Hypoglycemia may be more common in children than in adults treated with intensive insulin therapy and may interfere with attempts to improve diabetes control (9, 10). Although insulin pump therapy is effective and safe for many young people (11), not all children and adolescents are appropriate candidates for this method of treatment.

Insulin glargine is a new basal insulin manufactured by recombinant DNA technology. Modification of the structure of natural human insulin results in an analog that precipitates in the neutral environment of the subcutaneous tissue, leading to gradual absorption into the bloodstream. Studies via the euglycemic clamp method have shown that the onset of action following injection is about 2 h, the duration of action is about 24 h, and constant, peakless levels are maintained during the 24-h period (12, 13). Intersubject variability is lower than that seen with ultralente or neutral protamine Hagedorn (NPH) insulin and is comparable to the low variability seen with insulin pump therapy (13).

In this report, we describe a significant reduction in hemoglobin A1c levels over a 6-month period after switching from NPH insulin to insulin glargine in children and adolescents with poorly controlled type 1 diabetes.

Methods

Clinic population

The Fairview University of Minnesota Pediatric Diabetes Program manages approximately 250 patients with type 1 diabetes, 50 patients with type 2 diabetes, and 125 patients with cystic fibrosis-related diabetes. Intensive insulin treatment is recommended for all patients with type 1 diabetes, with a minimum of three or four insulin injections per day or insulin pump therapy. Patients whose hemoglobin A1c level is less than 9.0% are seen at 3-month intervals. Those with a hemoglobin A1c level greater than or equal to 9.0% are seen at 1- to 2-month intervals. A team approach is utilized, with a pediatric endocrinologist, diabetes nurse educator, dietitian and family therapist present at all clinic visits. The nurse educators spend extensive time outside of clinic providing telephone advice to patients. Hemoglobin A1c levels, the number of nurse calls since the last visit, and episodes of diabetic ketoacidosis (DKA) or severe hypoglycemia are routinely recorded at all clinic visits. Severe hypoglycemia is defined as hypoglycemia resulting in unconsciousness, seizure, or a level of obtundation severe enough that the patient requires assistance from another individual.

Subjects

During the 6-month period between 1 July 2001 and 31 December 2001, a clinical decision was made to switch patients with poorly controlled diabetes to insulin glargine in an effort to improve glycemic control. This change was recommended for patients with a hemoglobin A1c level greater than 8.0% who were not already on insulin pump therapy. One patient refused to make this switch, and the remaining 44 patients were started on insulin glargine therapy. Three of these subjects had diabetes of less than 1 yr duration with hemoglobin A1c levels still in the process of declining at the time of insulin glargine initiation. Four subjects, all of whom had a previous history of poor compliance with clinic visits, did not return to clinic during the 6-month follow-up period. Retrospective chart analysis was performed on the remaining cohort of 37 patients.

Initiation of insulin glargine therapy

Prior to initiation of insulin glargine therapy, all patients received NPH insulin two to three times per day and rapid-acting insulin (lispro or aspart) at mealtimes according to an individually determined insulin to carbohydrate ratio. To determine the insulin glargine dose, the total number of units of insulin per day was divided in half. Initially this was decreased by 20%, but it became apparent that this reduction was unnecessary. It was recommended that the insulin glargine be given pre-lunch, unless the family had a clear preference for another time of day, so that on school days the school nurse could supervise the injection.

This clinic routinely uses food records at least once a year to determine the insulin to carbohydrate ratio. Once insulin glargine was started, patients were asked to keep food records to re-evaluate this ratio on the new insulin. Rapid-acting insulin was prescribed based on the insulin to carbohydrate ratio at breakfast, lunch and supper, and, initially, for any snack containing greater than 30 g carbohydrate (not counting extra carbohydrates consumed to cover exercise).

A previous study, conducted in the General Clinical Research Center (GCRC) in men at rest, suggested that insulin glargine absorption is not affected by site since there was no difference between arm, abdomen or leg injections (14). However, because of concern that arm and leg absorption of insulin might be more variable in active children and because many children have very little subcutaneous fat in their extremities, we recommended that all insulin glargine injections be given in the abdomen or buttocks.

Assessment of psychosocial stress

A family therapist (TK) familiar with the patients but unaware of changes in hemoglobin A1c level rated the degree of psychosocial stress. One point each was given for: having a single parent; housing instability (living in a homeless shelter or moving more than once in the last year); severe parental discord or recent divorce; depression, eating disorder or other psychiatric illness in the child or parent; known drug or alcohol abuse in the child or parent; failing school; foster home placement; a recent death or other traumatic event in the family; development of a second serious illness in the preceding year (celiac disease, kidney or liver disease). This is not a validated measure of psychosocial stress, but it reflected the major stressors observed in our clinic population.

Analysis

Data are reported as means ± SD. Data were analyzed for differences between conditions at entry into the study and 6 months after the start of therapy by paired *t*-test. Comparisons of the characteristics between patients that showed a response to therapy and those who did not were made by *t*-test. Differences between categorical variables were investigated by Fisher's exact test. An α-value of 0.05 was used as the cut-off for statistical significance. The SAS® statistical package (SAS Institute, Cary, NC) was used for the statistical analysis.

Results

Subjects

Twenty-two girls and 15 boys were started on insulin glargine. The average age was 11.9 ± 3.9 yr and average duration of diabetes was 5.5 ± 3.8 yr.

The majority of patients (62%) were started on pre-lunch insulin glargine. Five per cent received the glargine before breakfast, 16% before dinner, and 16% at bedtime. Sixteen patients were started on insulin glargine in July, August or September, while 21 patients were started in October, November or December.

Hemoglobin A1c levels

The average hemoglobin A1c level at initiation of insulin glargine therapy was $10.1 \pm 2.0\%$. This was representative of the average hemoglobin A1c during the preceding 6-month period ($10.0 \pm 1.8\%$, average of 3 ± 1 measurements per subject). After 6 months of insulin glargine therapy, the average hemoglobin A1c level in the entire cohort had dropped to 8.9 ± 1.6 ($p = 0.001$). Improvement in hemoglobin A1c levels was most pronounced in those patients with the highest initial levels. The seven patients whose hemoglobin A1c was greater than 12.0% at baseline had an average fall of $3.5 \pm 1.9\%$ (Table 1).

Thirty patients responded to therapy with an average hemoglobin A1c drop of $1.7 \pm 1.5\%$, from 10.3 ± 2.2 to $8.6 \pm 1.5\%$ ($p < 0.001$). Seven patients did not respond to insulin glargine therapy, with an average hemoglobin A1c rise of $1.0 \pm 0.8\%$ from a baseline of $9.5 \pm 1.0\%$ to a level of $10.4 \pm 1.4\%$ ($p = 0.01$). Characteristics of the entire cohort, responders and non-responders are presented in Table 2. Gender, age at entry into the study and duration of diabetes were similar between the two groups ($p > 0.2$ for all comparisons, Fisher's for gender differences, *t*-test for age and duration of diabetes). Within each group, the number of clinic visits was no different before or after initiation of insulin glargine. There was an average of about one extra nurse call after starting the new therapy, which was expected, since patients were instructed to call during the first week for dosage adjustment. Of note, the non-responders had significantly fewer clinic visits than the responders both before and after starting insulin glargine therapy (1.9 ± 0.7 vs. 2.5 ± 1.2, $p = 0.01$) and significantly fewer phone conversations (1.1 ± 1.7 vs. 3.7 ± 4.9, $p = 0.02$).

Psychosocial stressors were not statistically higher in the non-responder group, although 57% of non-responder subjects had one or more major stressor identified in the previous yr compared to 37% of the responding patients ($p = 0.2$, Fisher's).

Table 1. Response to 6 months of insulin glargine therapy

Baseline HgbA1c (%)	Response to glargine	Number of subjects	HgbA1c change from baseline (mean ± SD)
8.1–9.0	↓ HgbA1c	10	-0.6 ± 1.0
	↑ HgbA1c	2	$+1.4 \pm 0.6$
9.1–10.0	↓ HgbA1c	8	-1.0 ± 1.1
	↑ HgbA1c	3	$+0.6 \pm 0.6$
10.1–12.0	↓ HgbA1c	5	-0.3 ± 1.4
	↑ HgbA1c	2	$+1.2 \pm 1.3$
12.1–15.1	↓ HgbA1c	7	-3.5 ± 1.9
	↑ HgbA1c	0	–

Table 2. Subject characteristics during the 6-month period before and the 6-month period after initiation of insulin glargine therapy. Data are reported for the entire cohort of patients (n = 37), those who responded with an improvement in hemoglobin A1c levels (n = 30), and those who did not respond with an improvement (n = 7). Mean ± SD

	Total	Responders	Non-responders
Age	11.9 ± 3.9	11.8 ± 3.6	12.6 ± 5.4
Tanner Stage	2.9 ± 1.8	2.9 ± 1.8	2.9 ± 2.0
Duration of diabetes (yr)	5.5 ± 3.8	5.8 ± 4.0	4.2 ± 5.4
% with one or more major stressors	41%	37%	57%
No. of clinic visits			
Pre	2.2 ± 1.4	2.3 ± 1.5	2.0 ± 0.8*
Post	2.4 ± 1.1	2.5 ± 1.2	1.9 ± 0.7*
No. of nurse calls			
Pre	2.4 ± 4.4	2.7 ± 4.8	1.0 ± 1.9*
Post	3.2 ± 4.5	3.7 ± 4.9	1.1 ± 1.7*
No. of episodes of DKA			
Pre	1	1	0
Post	0	0	0
No. of episodes of severe hypoglycemia			
Pre	0	0	0
Post	3	3	0

DKA, diabetic ketoacidosis.
*$p < 0.05$, responders vs. non-responders.

Adverse events

One patient had one episode of DKA in the 6-month period prior to initiation of insulin glargine therapy because he stopped taking insulin. There were no cases of DKA after starting insulin glargine.

While no episodes of severe hypoglycemia occurred pre-glargine therapy, there were three episodes after initiation of insulin glargine. Two of these occurred towards the end of the 6-month observation period and were associated with substantially increased levels of physical activity with no compensatory decrease in the insulin dose in patients whose baseline hemoglobin A1c level was > 11.0%. The third occurred in an adolescent who required psychological intervention because he became obsessive about maintaining extremely low blood glucose levels despite the objections of his parents and the medical team.

Patient acceptance

This regimen was well-accepted by patients, many of whom commented that they appreciated its flexibility. After the 6-month period, two patients chose to switch to insulin pump therapy while the remainder elected to stay on insulin glargine. Despite occasional reports that glargine injections were more uncomfortable, no patient chose to return to NPH insulin.

Discussion

This report documents improved glycemic control using insulin glargine therapy in poorly controlled children and adolescents with type 1 diabetes. Over a 6-month period, a statistically and clinically significant drop in hemoglobin A1c was seen in 81% of patients. Non-responders were characterized primarily by less frequent contact with the health care team both before and after the insulin change, and perhaps by more severe psychosocial stressors.

Previously, a large multicenter study compared bedtime insulin glargine with once or twice daily NPH insulin in 349 children aged 5–16 yr with type 1 diabetes (12, 15, 16). Regular insulin was given at meals. Over a 6-month period, there was a significant drop in fasting glucose levels, but the drop in hemoglobin A1c of 0.28 ± 0.09% from the baseline of 8.7% was not significant. There was a trend towards decreased severe hypoglycemia and decreased nocturnal severe hypoglycemia. In a follow-up study (17), 143 of these children continued to receive bedtime glargine and pre-meal regular insulin for a period of up to 36 months. Hemoglobin A1c remained at about 9% and the drug was well tolerated.

Twenty-six adolescents received 4 months of bedtime insulin glargine with pre-meal insulin lispro and 4 months of bedtime NPH with pre-meal regular insulin (18). Fasting glucose levels were lower on the glargine regimen, but the hemoglobin A1c level was not statistically different (8.7 vs. 9.1%). Asymptomatic hypoglycemia was 43% lower on the glargine regimen. Hypoglycemia was also less common in 30 children and adolescents 4–8 weeks after switching from two to four times daily NPH or lente insulin to glargine at bedtime (19).

In adult patients with type 1 diabetes, insulin glargine has been reported to result in better control of fasting blood glucose (20–23) and less frequent hypoglycemia (21) compared with NPH insulin. Hemoglobin A1c has been reported to be improved (20) or unchanged (21, 23) on glargine therapy. This insulin is also effective in patients with type 2 diabetes (24). Adults receiving

insulin glargine reported improved treatment satisfaction and improvements in general psychological well-being (25).

In contrast to previous studies in children and adults with type 1 diabetes, a significant reduction in hemoglobin A1c was found in the current report. We postulate two reasons for this. First, patients in this report were selected because they were in poor glycemic control whereas patients in previous studies were relatively well controlled, suggesting there was greater opportunity for major improvement. Second, and perhaps most important, the timing of insulin glargine administration needs to be considered. Supper and bedtime hours are often irregular or unsupervised in young people due to social and school activities or to a chaotic home environment. The noon-hour is a relatively stable mealtime for many children and adolescents, who have a scheduled, supervised lunch hour at school and who might wake up at noon on weekends. The current report describes an inner-city population in whom missed insulin injections are common and in whom parental supervision is often lacking. The practice of insulin glargine administration at lunchtime ensured that the school nurse could verify the child received the insulin. This is significant, since the glargine represented approximately half of the total daily insulin dose. Thus, the primary benefit of insulin glargine in the present study may have been related to the children actually receiving a greater portion of their prescribed insulin dose. This proposition is supported by the fact that the greatest improvement occurred in children with initial hemoglobin A1c levels $> 12\%$, which suggests a substantial number of missed insulin injections prior to study onset.

Unlike previous studies, which showed a reduced risk of hypoglycemia with insulin glargine, a greater degree of severe hypoglycemia was seen in the current cohort. In two cases, the hypoglycemia was associated with an increase in physical activity in children with a very high initial hemoglobin A1c level. It is likely that these patients had poorer compliance in general and paid less attention to adjusting insulin in response to changes in activity. Due to the nature of seasonal team sports, physical activity is much more variable in children than adults. A given sport tends to be available over roughly a 3-month period, with intensive tournament activity towards the end of the season followed by a period of inactivity until the next sport begins. It is critical that patients monitor glucose levels closely, as activity levels change, and that they maintain close contact with the health care team at these times.

In summary, the current retrospective study based on chart analysis describes the effectiveness of insulin glargine in lowering hemoglobin A1c levels in poorly controlled children and adolescents with type 1 diabetes. The response was particularly dramatic in children with hemoglobin A1c levels greater than 12% at baseline. Since 63% of subjects received insulin at lunchtime under the supervision of school nurses, the benefits of this therapy may have been primarily related to improved compliance with insulin administration. Larger, prospective studies are needed to confirm these findings and to explore the reasons for the improvement, but insulin glargine may offer an encouraging, practical option for treatment of these difficult patients.

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