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Glargine Versus NPH Insulin in Cystic Fibrosis Related Diabetes

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Abstract

Background—Cystic fibrosis related diabetes (CFRD) with fasting hyperglycemia is found in 15% of adult and 11% of adolescent CF patients. Because of concerns about hypoglycemia, it is not common practice to treat CFRD with 24-hour basal insulin therapy, despite evidence that insulin deficiency may contribute to protein catabolism and have an adverse effect on weight, muscle mass, pulmonary function, and, ultimately, survival. We hypothesized that insulin glargine would improve blood glucose control and weight in patients with CFRD without causing hypoglycemia.

Methods—A randomized cross-over study compared 12 weeks each of bedtime NPH or glargine in 19 CFRD patients.

Results—There was significantly greater reduction in fasting plasma glucose with glargine (P=0.03), and participants showed a non-significant trend towards weight gain with this insulin (P=0.07). No serious hypoglycemia occurred. At study end, all patients chose to continue glargine.

Conclusions—A study of longer duration is needed to determine whether insulin glargine impacts protein catabolism and overall clinical status in CF patients, but these initial data suggest that this is a promising therapy in CFRD.

Keywords

cystic fibrosis; CFRD; glargine

BACKGROUND

Cystic fibrosis related diabetes (CFRD) with fasting hyperglycemia occurs in about 15% of adult and 11% of adolescent patients (2). They are partially insulin deficient due to fibrotic pancreas damage, but enough endogenous insulin is generally present to prevent ketosis. Standard insulin therapy has focused on meal coverage; basal insulin is typically only

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Conflict of Interest

No conflict of interest exists. Sanofi Aventis funded the study but did not influence study design, data interpretation or manuscript preparation.

provided overnight in the form of NPH (3). Daytime basal insulin therapy is not usually prescribed based on the historical observation that most of these patients, unless they are acutely ill, are able to maintain normal blood glucose levels during the day as long as rapid-acting insulin is given with meals. In addition, daytime NPH may result in midday hypoglycemia in CFRD patients, because their fluctuating health status leads to unpredictable food intake and activity. We hypothesized that insulin glargine would improve blood glucose control and weight in patients with CFRD without causing hypoglycemia.

METHODS

Twenty adult patients with CFRD with FH were recruited. All were clinically well and receiving a single dose of bedtime NPH insulin plus rapid-acting insulin 3–6 times per day before meals.

Twelve week therapy with bedtime NPH was compared to 12 weeks of bedtime glargine in a randomized cross-over study. Before each study period there was a 1-month insulin adjustment period. Target glucose goals were 80–120mg/dl fasting and 80–150mg/dl 2h after meals. Insulin aspart was given pre-meal at least 3x/day according to the patient's individually established insulin:carbohydrate ratio and correction scale. The patient was in contact with the study nurse every 1–2 weeks for insulin adjustment.

Patients were seen in the GCRC at 0, 6 and 12 weeks, with time 0 starting at the end of the insulin adjustment month. Average fasting and 2hr post-dinner glucose levels by meter were calculated. Records and patient history were evaluated for hypoglycemia. Dual energy X-ray absorptiometry was employed to assess body composition.

Demographic characteristics of the two sequence groups (NPH-glargine and glargine-NPH) were compared using two-sample t-tests; gender proportions were compared using a chi-square test. Two models were fitted for each outcome, the first adjusting for period effect alone and the second adjusting for both period and baseline value, using a repeated-measures analysis of variance which included a test for differences between the sequence groups, that is, an interaction between sequence and treatment. Standard deviations of individual patient glucose monitor records were calculated from first differences (differences between consecutive records) to eliminate the effect of changes in the mean over time. Means are reported ± standard error of the mean.

RESULTS

Twenty subjects enrolled; one dropped out. There were 9 men and 10 women, age 34±8yrs with BMI 22.4±2.8 kg/m^2. Duration of diabetes was 9±5yrs and diabetes was well controlled (baseline HbA1c 6.5±0.1%). The group which received NPH first (n=9) was similar in demographic characteristics and gender proportion to the group which received glargine first.

There was no indication of an interaction between sequence (NPH-glargine, glargine-NPH) on outcome. Table 1 shows changes in study endpoints. Baseline values were associated with mean change in outcome and were used to adjust estimated mean changes. There was

significantly greater reduction in fasting plasma glucose during glargine treatment (*P*=0.03), but no differences in HbA1c or postprandial plasma glucose. Participants tended to gain more weight on glargine (*P*=0.07), but this was not significant and body composition was unchanged.

The average total daily insulin dose was 0.7 units/kg/day for each insulin. The insulin:carbohydrate ratios were 1.5±0.2 (NPH) and 1.3±0.1 (glargine) units insulin aspart/15 grams carbohydrate, *P*=0.05. Glargine was 46±4% and NPH 38±3% of the total daily insulin dose.

No difference in quality of life was seen. After the study was complete, all 19 patients chose to continue glargine therapy. The most common reason stated was that daytime blood glucose levels seemed more consistent. In addition, some patients were less worried about nighttime hypoglycemia. Despite patient perception, variability in glucose levels appeared to be similar between the treatment arms. The within-patient standard deviation of fasting glucose levels (NPH: 50±10 mg/dl, glargine: 40±6 mg/dl, *P*= 0.18) and 2h post-prandial glucose levels (NPH: 91±7 mg/dl, glargine: 83±6 mg/dl, *P*= 0.28) was not significantly different.

There was no difference in adverse events between study arms. No serious hypoglycemia occurred. Minor hypoglycemic episodes occurred 6±1 times per participant in the glargine arm and 5±1 times in the NPH arm, *P*=0.3.

CONCLUSIONS

We found significantly greater reduction in fasting plasma glucose with glargine compared to NPH in CF. Participants showed a non-significant tendency to gain weight, which we speculate might be related to the anabolic effect of continuous basal insulin coverage. These advantages were accomplished without an increase in the number or severity of hypoglycemic events. Glargine was well accepted by patients, each whom chose to remain on it at study end.

The standard practice of omitting daytime basal insulin in CFRD, based on practical considerations, ignores the relationship between insulin deficiency and clinical decline. Pulmonary function deteriorates more rapidly in CF patients with diabetes, and the annual rate of decline in lung function is directly related to the severity of insulin deficiency (4). Mortality is greater in CF patients who have diabetes compared to those who do not (5; 6). Survival in CF is well known to be dependent on good nutritional status, and insulin is a potent anabolic agent. Excessive protein catabolism (7; 8) and lipolysis (9) are seen even in clinically stable CF patients with abnormal glucose tolerance, and the resulting loss of weight and lean body mass may contribute to pulmonary disease and clinical decline. Thus, insulin replacement for anabolic purposes may be more important in CFRD than control of hyperglycemia.

The current study is limited by its relatively short duration, since the results might not have been sustained over a longer period. Also, there was no practical way to blind the study, and patients might have perceived an advantage because glargine was newer or they may have

been influenced by the healthcare team. Weight changes did not achieve statistical significance. Longterm studies are needed to determine the metabolic and nutritional impact of glargine in CFRD, but these initial data suggest that this is a promising therapy in CFRD.

Acknowledgments

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References

1. Cystic Fibrosis Foundation Patient Registry Annual Data Report. Bethesda, MD, 2004
2. Moran A, Doherty L, Wang X, Thomas W. Abnormal glucose metabolism in cystic fibrosis. J Pediatr. 1998; 133:10–16. [PubMed: 9672504]
3. Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, Brunzell C, Campbell PW, Chesrown SE, Duchow C, Fink RJ, FitzSimmons SC, Hamilton N, Hirsch I, Howenstine MS, Klein DJ, Madhun Z, Pencharz PB, Quittner AL, Robbins MK, Schindler T, Schissel K, Schwarzenberg SJ, Stallings VA, Tullis DE, Zipf WB. Diagnosis, screening, and management of CFRD: a consensus conference report. J Diabetes Research and Clinical Practice. 1999; 45:55–71.
4. Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in cystic fibrosis patients correlate with the degree of glucose intolerance at baseline. Am J Resp Crit Care Med. 2001; 162:891–895. [PubMed: 10988101]
5. Finkelstein SM, Wielinski CL, Elliott GR, Warwick WJ, Barbosa J, Wu SC, Klein DJ. Diabetes mellitus associated with cystic fibrosis. J Pediatr. 1988; 112:373–377. [PubMed: 3346774]
6. Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. Diabetes Care. 2005; 28:2141–2144. [PubMed: 16123480]
7. Moran A, Milla C, DuCret R, Nair KS. Protein metabolism in clinically stable adult CF patients with abnormal glucose tolerance. Diabetes. 2001; 50:1336–1343. [PubMed: 11375334]
8. Hardin DS, Leblanc A, Lukenbaugh S, Para L, Seilheimer DK. Proteolysis associated with insulin resistance in cystic fibrosis. Pediatrics. 1998; 101:433–437. [PubMed: 9481010]
9. Moran A, Basu R, Milla C, Jensen M. Insulin regulation of free fatty acid kinetics in adult cystic fibrosis patients with impaired glucose tolerance. Metabolism. 2004; 53:1467–1472. [PubMed: 15536603]

Table 1

Changes in study outcomes from baseline (the end of the 1-month insulin-adjustment phase of each arm) to week 12, adjusted for the baseline value of the outcome (presented in parentheses). Values are mean ± SEM, with negative changes indicating a decrease and positive changes an increase.

	Glargine	NPH	*P*
Hemoglobin A1c, %	−0.2±0.1 (6.4±0.2)	−0.2±0.1 (6.6±0.2)	.96
Fasting plasma glucose, mg/dl	−8±2 (123±4)	−0±2 (125±5)	.03
2h postprandial glucose, mg/dl	−6±5 (150 ± 6)	−8±5 (155±9)	.85
Weight, kg	+1.2±0.5 (64.3±2.4)	+0.2±0.5 (65.7±2.5)	.07
Fat mass by DEXA, kg	+0.7±0.4 (16.1±1.4)	+0.4±0.4 (16.7±1.5)	.09
Lean mass by DEXA, kg	+0.3±0.2 (45.7±1.9)	+0.1±0.2 (45.7±2.0)	.50