Terbutaline and the Prevention of Nocturnal Hypoglycemia in Type 1 Diabetes

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Objective – Bedtime administration of 5.0 mg of the β2-adrenergic agonist terbutaline prevents nocturnal hypoglycemia but causes morning hyperglycemia in type 1 diabetes. We tested the hypothesis that 2.5 mg of terbutaline prevents nocturnal hypoglycemia without causing morning hyperglycemia.

Research Design and Methods – Randomized, double blind, crossover pilot study – placebo, terbutaline 2.5 mg, terbutaline 5.0 mg – in 15 patients with type 1 diabetes.

Results – Mean (±SE) nadir nocturnal plasma glucose concentrations were 87±14 mg/dL following placebo, 100±14 mg/dL following terbutaline 2.5 mg and 122±13 mg/dL following terbutaline 5.0 mg (P<0.05 vs. placebo). Nadir levels were <50 mg/dL in 5, 2 and 0 patients (P<0.05 vs. placebo) respectively. Morning levels were 113±18, 127±17 and 183±19 mg/dL (P<0.02 vs. placebo) respectively.

Conclusions – Terbutaline may be shown to be effective and safe in the prevention of nocturnal hypoglycemia in type 1 diabetes in a suitably powered randomized controlled trial.
Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes (1). Most episodes of hypoglycemia occur at night, specifically during sleep, in type 1 diabetes, a finding in the Diabetes Control and Complications Trial (2) that continues to be documented (3,4). Sympathoadrenal responses to hypoglycemia are reduced further during sleep (5,6) and, probably because of their markedly reduced sympathoadrenal responses, patients with type 1 diabetes are substantially less likely to be awakened by hypoglycemia than nondiabetic individuals (6,7).

Among the approaches to the prevention of nocturnal hypoglycemia in type 1 diabetes, we found bedtime administration of a conventional snack, of uncooked cornstarch, or of an α-glucosidase inhibitor to be ineffective (3). In contrast, bedtime administration of the epinephrine simulating β2-adrenergic agonist terbutaline in a dose of 5.0 mg prevented nocturnal hypoglycemia (3). However, it also caused hyperglycemia the following morning. Therefore, we used a randomized, double blind, crossover design – placebo, terbutaline 2.5 mg and terbutaline 5.0 mg – in a pilot study to test the hypothesis that bedtime administration of 2.5 mg of terbutaline prevents nocturnal hypoglycemia without causing morning hyperglycemia in patients with aggressively treated type 1 diabetes.

RESEARCH DESIGN AND METHODS

**Subjects.** Fifteen patients (7 women) with type 1 diabetes gave their written consent to participate in this study which was approved by the Washington University Human Research Protection Office and conducted at the institution’s General Clinical Research Center (GCRC). Their mean (±SD) age was 28.6±7.5 years, body mass index 29.3±5.6 kg/m², duration of type 1 diabetes 14.9±7.0 years and HbA1C 7.1±0.5%. They were selected for a HbA1C ≤8.0% and the absence of complications of diabetes or use of a potentially interfering medication. Nine were using continuous subcutaneous insulin infusion with insulin analogues and six were using multiple daily injection with insulin analogues aside from one using basal NPH insulin and one using prandial regular insulin.

**Experimental Design.** As in our earlier study (3), the patients pursued their usual activities and used their individual treatment regimens with guidance from their individual caregivers throughout the study. They were admitted to the GCRC early in the evening on three occasions. Venous blood samples, for plasma glucose measurements (YSI Glucose Analyzer, Yellow Springs Instruments Corp., Yellow Springs, OH), were drawn at 15 minutes intervals from 2200h through 0700h. Glucose levels <40 mg/dL were treated with small doses of intravenous glucose (3).

One of three oral bedtime treatments was administered, in random sequence and in double blind fashion, at 2200h. These included: 1) placebo, 2) terbutaline (Brethine, Novartis Pharmaceuticals Corp., East Hanover, NJ), 2.5 mg and 3) terbutaline, 5.0 mg.

**Statistical Methods.** The data are expressed as the mean and the standard error (SE) except where the standard deviation (SD) is specified. Time and condition related data were analyzed by mixed model repeated measures analysis of variance (ANOVA). Contrasts of interest were assessed with a t-test. P values <0.05 were considered to indicate...
statistically significant differences.

RESULTS

Bedtime terbutaline 5.0 mg, but not 2.5 mg, raised mean plasma glucose concentrations during the night (ANOVA P<0.01) (data not shown). Nadir nocturnal plasma glucose concentrations were <70 mg/dL in 7 (47%) patients, <60 mg/dL in 6 (40%), <50 mg/dL in 5 (33%) and <40 mg/dL in 2 (13%) following bedtime placebo. The corresponding numbers were 7, 6, 2 and 0 patients following terbutaline 2.5 mg and 3, 0 (P<0.02 vs. placebo), 0 (P<0.05 vs. placebo) and 0 patients following terbutaline 5.0 mg.

Mean nadir plasma glucose concentrations were 87±14 mg/dL following placebo, 100±14 mg/dL following terbutaline 2.5 mg and 122±13 mg/dL following terbutaline 5.0 mg (P<0.05 vs. placebo) (Figure). Mean 0700h glucose levels were 113±18, 127±17 and 183±19 mg/dL (P<0.02 vs. placebo) respectively (Figure). Mean 0700h heart rates were 78±5, 82±4 and 88±5 (P<0.02 vs. placebo) bpm respectively. Terbutaline was seemingly well tolerated.

CONCLUSIONS

These data also confirm that bedtime administration of 5.0 mg of the epinephrine simulating β2-adrenergic agonist terbutaline effectively prevents nocturnal hypoglycemia in patients with aggressively treated type 1 diabetes (3). That dose of terbutaline increased plasma glucose concentrations throughout the night, raised the nocturnal nadir plasma glucose concentration significantly and eliminated nocturnal plasma glucose concentrations less than 60 mg/dL. However, as in our earlier study (3), it caused hyperglycemia the following morning.

Here we tested the hypothesis that bedtime administration of 2.5 mg of terbutaline prevents nocturnal hypoglycemia without causing hyperglycemia the following morning. That hypothesis was not confirmed statistically in this small sample. However, the key efficacy endpoints – the number of patients with nocturnal plasma glucose concentrations <50 mg/dL and the mean nadir nocturnal plasma glucose concentration – were intermediate between those following bedtime placebo and following bedtime terbutaline 5.0 mg. Documentation of the efficacy and safety of bedtime administration of terbutaline in the prevention of nocturnal hypoglycemia in patients with type 1 diabetes will require a suitably powered randomized controlled trial of relatively long-term terbutaline administration.

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Disclosures

P.E.C. has consulted for Merck & Co., Marcadia Biotech, Novo Nordisk, Johnson & Johnson, MannKind, Medtronic MiniMed, Takeda, and TolerRx in recent years. B.A.C., S.M.B., and A.M.A. have nothing to disclose.
REFERENCES
1. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 350:2272-2279, 2004.
2. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271-286, 1997.
3. Raju B, Arbelaez AM, Breckenridge SM, Cryer PE. Nocturnal hypoglycemia in type 1 diabetes: An assessment of preventive bedtime treatments. *J Clin Endocrinol Metab* 91:2087-2092, 2006.
4. Wenthol IME, Maran A, Masurel N, Heine RJ, Hoekstra JBL, DeVries JH. Nocturnal hypoglycaemia in type 1 diabetic patients, assessed with continuous glucose monitoring: frequency, duration and associations. *Diabet Med* 24:527-532, 2007.
5. Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV. Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med* 338:1657-1662, 1998.
6. Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: Reduced awakening from sleep during hypoglycemia. *Diabetes* 52:1195-1203, 2003.
7. Schultes B, Jauch-Chara K, Gais S, Hallschmid M, Reiprich E, Kern W, Oltmanns KM, Peters A, Fehm HL, Born J. Defective awakening response to nocturnal hypoglycemia in patients with type 1 diabetes mellitus. *PLoS Medicine* 4:e69, 2007.
8. American diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes. *Diabetes Care* 28:1245-1249, 2005.
Figure Legend

Figure. Mean (±SE) bedtime (2200h), nocturnal nadir and morning (0700h) plasma glucose concentrations following bedtime oral administration of placebo, terbutaline 2.5 mg or terbutaline 5.0 mg in 15 patients with type 1 diabetes. *P<0.05 vs. placebo. **P<0.02 vs. placebo.