Terbutaline and the Prevention of Nocturnal Hypoglycemia in Type 1 Diabetes

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OBJECTIVE — Bedtime administration of 5.0 mg of the β_2-adrenergic agonist terbutaline prevents nocturnal hypoglycemia but causes morning hyperglycemia in type 1 diabetes. We tested the hypothesis that 2.5 mg terbutaline prevents nocturnal hypoglycemia without causing morning hyperglycemia.

RESEARCH DESIGN AND METHODS — This was a randomized double-blind crossover pilot study (placebo, 2.5 mg terbutaline, and 5.0 mg terbutaline) 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 2.5 mg terbutaline, and 122 ± 13 mg/dl following 5.0 mg terbutaline ($P < 0.05$ 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.

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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, uncooked cornstarch, or an α-glucosidase inhibitor to be ineffective (3). In contrast, bedtime administration of the epinephrine-simulating β_2-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, 2.5 mg terbutaline, and 5.0 mg terbutaline) in a pilot study to test the hypothesis that bedtime administration of 2.5 mg terbutaline prevents nocturnal hypoglycemia without causing morning hypoglycemia in patients with aggressively treated type 1 diabetes.

RESEARCH DESIGN AND METHODS

— Fifteen patients (seven 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. Mean ± SD age was 28.6 ± 7.5 years, BMI 29.3 ± 5.6 kg/m^2, duration of type 1 diabetes 14.9 ± 7.0 years, and A1C 7.1 ± 0.5%. Subjects were selected for an A1C ≤8.0% and the absence of diabetes complications or use of a potentially interfering medication. Nine subjects were using continuous subcutaneous insulin infusion with insulin analogs, and six were using multiple daily injection with insulin analogs (aside from one using basal NPH insulin and one using prandial regular insulin).

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 Washington University General Clinical Research Center early in the evening on three occasions. Venous blood samples for plasma glucose measurements (YSI Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, OH) were drawn at 15-min intervals from 2200 h through 0700 h. 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 2200 h. These included placebo, 2.5 mg terbutaline (Brethine; Novartis Pharmaceuticals, East Hanover, NJ), and 5.0 mg terbutaline.

Statistical methods

Data are expressed as means ± SE except where SD is specified. Time- and condition-related data were analyzed by mixed-model repeated-measures ANOVA. Contrasts of interest were assessed with a *t* test. *P* values < 0.05 were considered to indicate statistically significant differences.

RESULTS

— Bedtime administration of 5.0 mg terbutaline, but not 2.5 mg, raised mean plasma glucose concentrations during the night (ANOVA $P < 0.01$)

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P.E.C. has consulted for Merck & Co., Marcadia Biotech, Novo Nordisk, Johnson & Johnson, MannKind, Medtronic MiniMed, Takeda, and TolerRx in recent years.

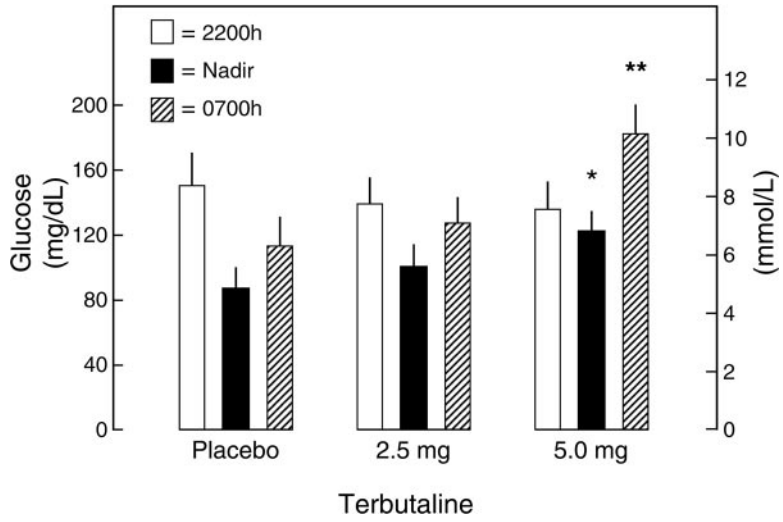

Fig. 1—*Mean ± SE bedtime (2200 h), nocturnal nadir, and morning (0700 h) plasma glucose concentrations following bedtime oral administration of placebo, 2.5 mg terbutaline, or 5.0 mg terbutaline in 15 patients with type 1 diabetes.* *P < *0.05 vs. placebo.* **P < *0.02 vs. placebo.*

(data not shown). Nadir nocturnal plasma glucose concentrations were <70 mg/dl in seven patients (47%), <60 mg/dl in six (40%), <50 mg/dl in five (33%), and <40 mg/dl in two (13%) following bedtime placebo. Corresponding nadir nocturnal concentrations were seen in seven, six, two, and zero patients, respectively, following administration of 2.5 mg terbutaline and in three, zero ($P < 0.02$ vs. placebo), zero ($P < 0.05$ vs. placebo), and zero patients following administration of 5.0 mg terbutaline.

Mean nadir plasma glucose concentrations were 87 ± 14 mg/dl following placebo, 100 ± 14 mg/dl following 2.5 mg terbutaline, and 122 ± 13 mg/dl following 5.0 mg terbutaline ($P < 0.05$ vs. placebo) (Fig. 1). Mean 0700 h glucose levels were 113 ± 18, 127 ± 17, and 183 ± 19 mg/dl ($P < 0.02$ vs. placebo), respectively (Fig. 1). Mean 0700 h heart rates were 78 ± 5, 82 ± 4, and 88 ± 5 bpm ($P < 0.02$ vs. placebo, respectively). Terbutaline was seemingly well tolerated.

CONCLUSIONS — These data confirm a high frequency of nocturnal hypoglycemia in patients with aggressively treated type 1 diabetes (1–4). In the absence of an active bedtime treatment (placebo administration), nadir nocturnal plasma glucose concentrations were <70 mg/dl (3.9 mmol/l), the alert value recommended by the American Diabetes Association Workgroup on Hypoglycemia (8), in 7 of 15 patients (47%). They were <60 mg/dl (3.3 mmol/l) in six patients (40%), <50 mg/dl (2.8 mmol/l) in five patients (33%), and <40 mg/dl (2.2 mmol/l) in two patients (13%).

These data also confirm that bedtime administration of 5.0 mg of the epinephrine-simulating β_2-adrenergic agonist terbutaline effectively prevents nocturnal hypoglycemia in patients with aggressively treated type 1 diabetes (3) and 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 <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 terbutaline prevents nocturnal hypoglycemia without causing hyperglycemia the following morning. That hypothesis was not confirmed statistically in this small sample. However, the key efficacy end points, the number of patients with nocturnal plasma glucose concentrations <50 mg/dl and the mean nadir nocturnal plasma glucose concentration, were intermediate between those taking placebo at bedtime and those taking 5.0 mg terbutaline at bedtime. 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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