# Voglibose Administration Before the Evening Meal Improves Nocturnal Hypoglycemia in Insulin-Dependent Diabetic Patients With Intensive Insulin Therapy

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**Nocturnal hypoglycemia is one of the serious complications of intensive insulin therapy in patients with insulin-dependent diabetes mellitus (IDDM; type 1 DM). We assessed the effect of voglibose (α-glucosidase inhibitor) administration before the evening meal on nocturnal hypoglycemia in IDDM patients with intensive insulin therapy. Ten IDDM patients received 0.3 mg voglibose just before the evening meal for 5 days. The diet and insulin regimen were not changed throughout the study. Nocturnal plasma glucose levels (10 PM, 3 AM, and 7 AM) were studied in these patients before and during voglibose administration. Blood glucose levels were measured at 3 AM before and during voglibose treatment. The mean plasma glucose level at 3 AM was 3.4 ± 0.4 mmol/L before voglibose treatment and 7.3 ± 1.0 mmol/L during treatment. Plasma glucose at 3 AM was elevated in 9 of 10 patients with voglibose. The decrease in plasma glucose from 10 PM to 3 AM was 6.5 ± 0.8 mmol/L before voglibose administration but 3.2 ± 0.9 mmol/L during treatment ($P < .01$). The hypoglycemia rate was 52% (17 of 33 nights) before voglibose administration but only 9.1% (3 of 33 nights) during treatment. We conclude that voglibose administration before the evening meal improves nocturnal hypoglycemia in IDDM patients with intensive insulin therapy.**


INTENSIVE INSULIN THERAPY delays the onset of diabetic complications and may improve their progression in patients with insulin-dependent diabetes mellitus (IDDM; type 1 DM).[1] However, patients receiving intensive insulin therapy may develop severe hypoglycemia.[1] Hypoglycemia stimulates the release of epinephrine, glucagon, cortisol, and growth hormone into the blood; these counterregulatory hormones increase the blood glucose level. In IDDM patients, epinephrine is released more prominently than glucagon. This epinephrine release may induce adrenergic symptoms, which include pallor, sweating, tachycardia, tremor, anxiety, and hunger. These adrenergic symptoms portend hypoglycemia while simultaneously contributing to glucose counterregulation. Sleep impairs the epinephrine response to hypoglycemia; epinephrine does not increase much during sleep. Sleep also masks the adrenergic symptoms. Thus, during sleep, some hypoglycemic patients are not aware of their hypoglycemia. Therefore, it is important to prevent nocturnal hypoglycemia during sleep.[2-6]

Voglibose inhibits α-glucosidase activity in the small intestine and delays the postprandial absorption of sucrose. Usually, the upper small intestine absorbs sucrose. Voglibose inhibits this sucrose absorption in the upper small intestine; thus, the lower small intestine absorbs sucrose after voglibose administration.[7] Therefore, we would predict that plasma glucose levels would be elevated after 6 to 8 hours with voglibose treatment before meals.

We studied the effects of voglibose administration before the evening meal on plasma glucose levels in IDDM patients with intensive insulin therapy. We expected an improvement of the nocturnal hypoglycemia after voglibose administration before the evening meal.

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## SUBJECTS AND METHODS

### *Subjects*

We studied 10 IDDM patients who received 4 daily insulin injections and had a history of nocturnal hypoglycemia, and who had many episodes of nocturnal hypoglycemia with the bedtime snack and insulin reduction during the first 2 weeks of their hospital stay (Table 1). All 10 patients received regular insulin 3 times per day and NPH insulin at bedtime (10 PM). Regular insulin was injected in the abdominal wall, and NPH insulin in the thigh. Urinary C-peptide levels were low (0 to 11.4 μg/d). Three of 10 patients had no retinopathy, but the others did have retinopathy. Eight of 10 patients had no clinical nephropathy (Mogensen's criteria, <III).[8] Three of 10 patients had no clinical evidence of diabetic polyneuropathy based on history and physical examination. Autonomic functions were assessed by heart rate changes during deep breathing ($CV_{R-R}$) and blood pressure responses to orthostatic changes (ΔBP). $CV_{R-R}$ should be less than 1.0% and ΔBP should be greater than 30 mm Hg when a patient does not have abnormal autonomic function. Informed consent was obtained from all patients.

### *Study Design*

The diet and insulin regimen were individualized for each patient. The caloric distribution was as follows: carbohydrate 50%, fat 30%, and protein 20%. The insulin regimens were not changed throughout the study. Nocturnal plasma glucose levels (10 PM, 3 AM, and 7 AM) were measured on the day before voglibose treatment. Voglibose (0.3 mg) was administered just before the evening meal for 5 days. On day 5 (during voglibose administration), nocturnal plasma glucose levels (10 PM, 3 AM, and 7 AM) were measured. In addition, the blood glucose level was measured at 3 AM before and during voglibose treatment on at least 1 night.

### *Analytical Methods*

The plasma glucose level was measured by the hexokinase method. Glycosylated hemoglobin was determined by high-performance liquid chromatography (Kyoto Daiichi Kagaku, Kyoto, Japan). Urinary C-peptide was determined by radioimmunoassay (Daiichi Radioisotope, Tokyo, Japan). The blood glucose level was measured by an enzyme electrode (Kyoto Daiichi Kagaku).

**Table 1. Characteristics of IDDM Patients With Intensive Insulin Therapy**

| Patient No. | Age (yr)/ Sex | Duration of IDDM (yr) | Body Mass Index (kg/m²) | Total Insulin (U/kg) NPH (U) | Hemoglobin $A_{1c}$ (%) | Retinopathy | $CV_{R-R}$ (%) | Δ BP (mm Hg) | Nephropathy (grade) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 61/M | 4 | 21.9 | 0.72/20 | 7.4 | None | 1.3 | −30 | II |
| 2 | 35/M | 1 | 19.6 | 0.43/8 | 7.3 | BDR | 12 | −20 | I |
| 3 | 43/M | 18 | 23.7 | 0.43/4 | 8.3 | None | 3.9 | −17 | II |
| 4 | 60/M | 10 | 18.8 | 0.86/7 | 12.4 | PPDR | 1.6 | −18 | II |
| 5 | 22/F | 16 | 23.1 | 0.62/4 | 13.9 | PPDR | 4.3 | −5 | IV |
| 6 | 35/F | 22 | 21.4 | 0.52/6 | 10.3 | BDR | 2.7 | — | IV |
| 7 | 16/F | 5 | 22.6 | 0.86/10 | 9.9 | BDR | — | −5 | II |
| 8 | 21/F | 9 | 18.9 | 1.53/30 | 7.9 | BDR | 3.9 | — | II |
| 9 | 72/F | 17 | 26.0 | 0.43/6 | 8.9 | PPDR | 1.5 | −35 | II |
| 10 | 68/F | 1 | 22.4 | 0.79/10 | 8.5 | None | — | −10 | I |

NOTE. BDR (background diabetic retinopathy) indicates the presence of microaneurysms plus mild to moderate retinal hemorrhages or hard exudates. PPDR (preproliferative diabetic retinopathy) indicates the presence of microaneurysms plus any of the following: cotton-wool spots, mild intraretinal microvascular abnormalities or venous beadings, or increased capillary occlusions. Autonomic functions were studied by measuring heart rate variations during deep breathing (positive, $CV_{R-R}$ <1.0%) and blood pressure responses to orthostatic changes (positive, Δ BP >30 mm Hg). Nephropathy was classified according to Mogensen.[8]

*Statistical Analysis*

Values are the mean ± SE. Comparisons between groups were assessed by paired *t* test and chi-square test. A *P* value less than .05 was considered statistically significant.

## RESULTS

*Plasma Glucose*

Plasma glucose levels were lower at 3 AM versus 10 PM and 7 AM in all 10 patients before and during voglibose treatment (Fig 1). The mean plasma glucose level at 3 AM was 3.4 ± 0.4 mmol/L before voglibose administration and 7.3 ± 1.0 mmol/L during treatment; the latter plasma glucose values were significantly higher ($P < .05$) than the former values. No significant differences were noted between the mean plasma glucose levels at 10 PM and 7 AM before and during voglibose administration. Figure 2 demonstrates that plasma glucose levels at 3 AM were higher during voglibose administration than pretreatment levels in 9 of 10 patients studied. Nocturnal plasma glucose was 1.8 mmol/L before voglibose treatment in 2 patients; it increased to 4.6 mmol/L in 1 patient and 6.4 mmol/L in the other during treatment.

*Differences in Glucose Levels*

Figure 3 demonstrates the decrease of plasma glucose from 10 PM to 3 AM, and the increase from 3 AM to 7 AM. The decrease in plasma glucose from 10 PM to 3 AM was 6.5 ± 0.8 mmol/L before voglibose administration but 3.2 ± 0.9 mmol/L during treatment ($P < .01$). The increase in plasma glucose from 3 AM to 7 AM was 6.2 ± 1.2 mmol/L pretreatment but 2.7 ± 1.3 mmol/L during treatment ($P < .05$; Fig 3). Voglibose administration reduced the change in plasma glucose levels. There was no significant association between the change in glucose levels and diabetic complications (data not shown).

*Hypoglycemia Before and During Voglibose Administration*

The patients had episodes of hypoglycemia (defined as blood glucose <3.9 mmol/L) on 17 nights (52%) before voglibose administration (Table 2). However, the patients had episodes of hypoglycemia on only 3 nights (9.1%) during voglibose administration. The nocturnal episodes of hypoglycemia were significantly fewer during voglibose treatment versus pretreatment (chi-square test, $P < .05$).

## DISCUSSION

Voglibose administration before the evening meal improves nocturnal hypoglycemia. McCulloch et al[9] showed that acar-

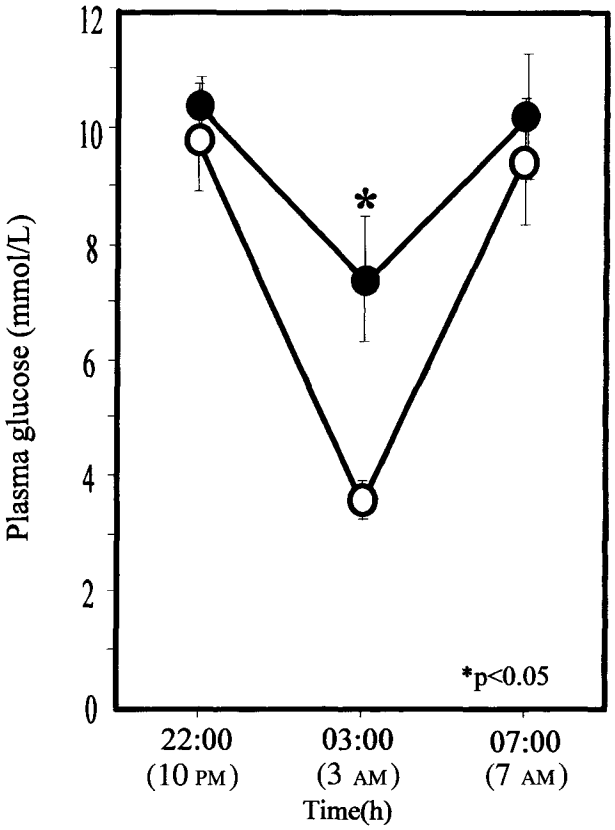


**Fig 1. Mean nocturnal plasma glucose levels before (○) and during (●) voglibose administration. Values are the mean ± SE of 10 patients. Plasma glucose was significantly higher at 03:00h (3 AM) during voglibose treatment *v* before treatment.**

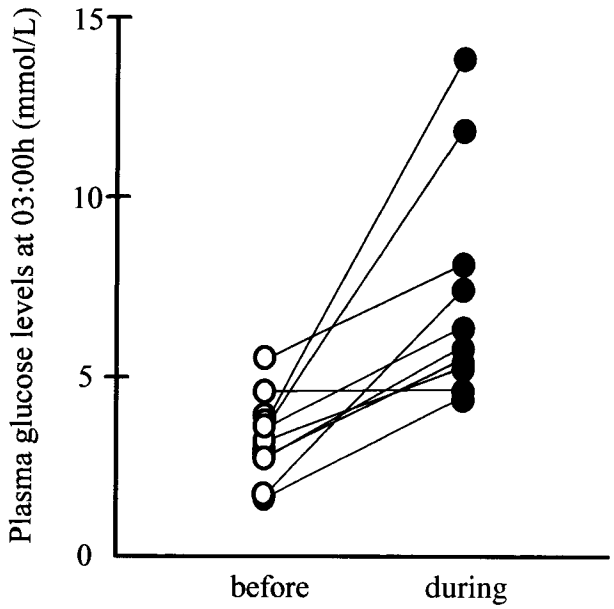


**Fig 2. Plasma glucose levels at 03:00h (3 AM) before (○) and during (●) voglibose administration in 10 IDDM patients with intensive insulin therapy.**

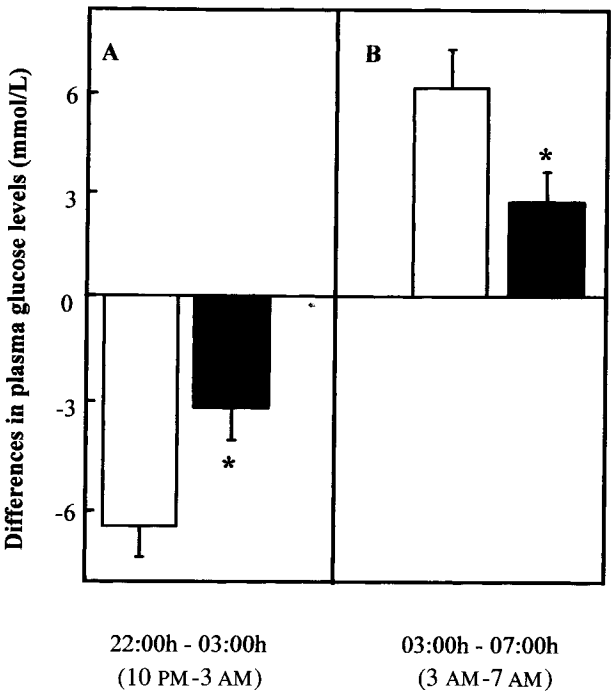


**Fig 3. Decrease (A) and increase (B) in plasma glucose levels before (□) and during (■) voglibose administration. The decrease in plasma glucose from 22:00h (10 PM) to 03:00h (3 AM) is shown in A. The increase in plasma glucose from 03:00h (3 AM) to 07:00h (7 AM) is shown in B. Values are the mean ± SE of 10 patients. *$P < .05$, before *v* during voglibose treatment.**

bose administration with the bedtime snack can markedly reduced the frequency of symptomatic nocturnal hypoglycemia in IDDM patients treated with conventional insulin therapy. Acarbose and voglibose inhibit α-glucosidase in the small intestine. They delay the postprandial absorption of sucrose.[10] Acarbose reduces the total caloric intake by approximately 30%.[11,12] In a previous study, simultaneous administration of sucrose and voglibose at low doses (0.03 mg/kg) in rats delayed sucrose absorption; sucrose was detected in the middle and lower sections of the small intestine after 3 hours, but it was scarcely detected in any part of the gastrointestinal tract after 6 hours.[7] In short, voglibose delayed the absorption of sucrose without a change in the overall caloric intake.[13] We expected that plasma glucose levels would increase after 6 to 8 hours with voglibose treatment. Thus, we studied the effects of voglibose administration before the evening meal on plasma glucose at 3 AM. Voglibose treatment improved nocturnal hypoglycemia.

Plasma glucose levels were lower at 3 AM versus 10 PM and 7 AM. Voglibose increased plasma glucose levels at 3 AM significantly, even without a bedtime snack. Voglibose administration reduced the decrease in plasma glucose and the frequency of hypoglycemia. Thus, voglibose treatment before the evening meal improved nocturnal hypoglycemia. Nine of 10 patients did not have nocturnal hypoglycemia during voglibose administration. There were no significant differences in the age, sex, body mass index, duration of diabetes, presence or absence of complications, and hemoglobin $A_{1c}$ between 9 patients without hypoglycemia and 1 patient with hypoglycemia during voglibose administration.

We expected that voglibose treatment would decrease the next morning plasma glucose. However, no significant differences in morning plasma glucose were noted before versus during voglibose administration. Axelsen et al[14] evaluated the effect of uncooked cornstarch (slow-release carbohydrate) at bedtime on nocturnal glucose in non–insulin-dependent diabetic patients. There was no decrease in fasting glucose after the cornstarch meal, due to the persistent nocturnal elevation in glucose. In our study, nocturnal plasma glucose levels showed a similar V-shaped pattern before and during voglibose administration. There was no decrease in fasting plasma glucose during voglibose treatment by the "dawn phenomenon."

A bedtime snack was chosen to prevent nocturnal hypoglycemia. A bedtime snack may increase plasma glucose; however, the effects may be transient. It should also be noted that a bedtime snack increases the total caloric intake. To improve nocturnal hypoglycemia in insulin-treated IDDM patients, we recommend voglibose administration instead of a bedtime snack, since the former does not increase total caloric intake but the latter does.

**Table 2. Hypoglycemia Before and During Voglibose Administration**

| | Voglibose Administration | | |
|---|---|---|---|
| | Before | During | Total |
| Hypoglycemia* | | | |
| Present | 17 (52%) | 3 (9%) | 20 (30%) |
| Absent | 16 (48%) | 30 (91%) | 46 (70%) |
| Total | 33 | 33 | 66 |

NOTE. The nocturnal episodes of hypoglycemia are shown. The episodes were significantly less frequent during voglibose treatment than before treatment (chi-square test, $P < .05$).

*Defined as blood glucose <3.9 mmol/L.

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