

# Control of Postprandial Plasma Glucose by an Oral Insulin Product (HIM2) in Patients With Type 2 Diabetes

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postprandial glycemia without causing peripheral hyperinsulinemia in patients with type 2 diabetes.

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**OBJECTIVE** — The objectives of this exploratory study were to assess the postprandial glucose-lowering effects and evaluate the safety and tolerability of single, escalating doses of an oral insulin product, hexyl-insulin monoconjugate 2 (HIM2), in patients with type 2 diabetes. Subcutaneous insulin and oral placebo were also administered for comparison.

**RESEARCH DESIGN AND METHODS** — Eighteen patients with type 2 diabetes were enrolled in this randomized, single-blind, placebo-controlled, three-way crossover, dose-escalation study. A single dose of each of the following study drugs was administered to each patient on 3 separate days: oral HIM2 (at one of three dose levels: 0.375, 0.5, or 1.0 mg/kg), subcutaneous regular insulin (8 units Humulin R), and oral placebo. At 30 min after dosing, patients ingested a standardized test meal (16 oz/720 calories of Boost Plus). Serial blood samples were collected for determination of plasma glucose and insulin concentrations during the 4-h postdose period.

**RESULTS** — The mean glucose area under the curve for 0 to 240 min ( $AUC_{0-240}$ ) values were lower following administration of 0.5 and 1.0 mg/kg HIM2 vs. placebo (1,097.1 vs. 1,196.9 and 801.1 vs. 992.1  $mg \cdot h^{-1} \cdot dl^{-1}$ , respectively). This difference was statistically significant at the 1.0-mg/kg HIM2 dose level. Insulin exposure, as measured by insulin  $AUC_{0-240}$  values, for the 0.375-, 0.5-, and 1.0-mg/kg dose levels of HIM2 were 169.9, 193.1, and 230.8  $\mu U \cdot h^{-1} \cdot ml^{-1}$ , respectively; insulin  $AUC_{0-240}$  values for placebo were 165.8, 196.1, and 169.2  $\mu U \cdot h^{-1} \cdot ml^{-1}$ , respectively. The mean glucose  $AUC_{0-240}$  values were similar following administration of 0.5 and 1.0 mg/kg HIM2 vs. subcutaneous insulin (1,097.1 vs. 1,048.0 and 801.1 vs. 875.2  $mg \cdot h^{-1} \cdot dl^{-1}$ , respectively). For pooled data from the 0.5- and 1.0-mg/kg dose groups, the HIM2/subcutaneous insulin ratios for the 2-h postprandial glucose concentration (0.97, 95% CI 0.90–1.06), maximum postprandial glucose concentration (0.99, 95% CI 0.93–1.06), and glucose  $AUC_{0-240}$  (0.98, 95% CI 0.9–1.06) were within 10% of unity, implying glucodynamic equivalence. Although HIM2 (0.5 and 1.0 mg/kg) and subcutaneous insulin (8 units) provided comparable control of postprandial plasma glucose concentrations, HIM2 resulted in peripheral insulin concentrations that were lower than subcutaneous insulin (mean insulin  $AUC_{0-240}$  of 193.1 vs. 233.6 and 230.8 vs. 270.3  $\mu U \cdot h^{-1} \cdot ml^{-1}$ , respectively).

**CONCLUSIONS** — Single, oral doses of HIM2 were safe and well tolerated. HIM2 (0.5 and 1.0 mg/kg) was more effective than placebo and as effective as subcutaneous regular insulin (8 units) at controlling postprandial glycemia with respect to the following parameters: 2-h postprandial glucose concentration, maximum glucose concentration, and glucose  $AUC_{0-240}$ . This occurred even though peripheral insulin concentrations were lower following the administration of HIM2 (0.5 and 1.0 mg/kg) than subcutaneous insulin. Thus, HIM2 therapy may control

inadequate control of hyperglycemia in patients with type 2 diabetes is associated with severe microvascular and macrovascular complications (1–4). Clinical studies demonstrated that tight control of fasting and postprandial glycemia in patients with type 2 diabetes resulted in dramatic reductions in the incidence and rate of progression of microvascular complications (5,6).

To adequately control postprandial glycemia, several daily injections of insulin are necessary. However, insulin therapy via subcutaneous or other parenteral routes is known to result in peripheral hyperinsulinemia. In addition to the risk of hypoglycemia, some studies have suggested that peripheral hyperinsulinemia may be associated with coronary artery disease, hypertension, dyslipidemia, and weight gain (7–10). There is strong evidence suggesting that an oral insulin product would provide insulin in a more physiologic manner, with a resultant decrease in peripheral insulin concentrations, and that it would more adequately “insulinize” the liver (11,12).

Nobex Corp. has developed hexyl-insulin monoconjugate 2 (HIM2), in which a single amphiphilic oligomer is covalently linked to the free amino group on the Lys- $\beta$ 29 residue of recombinant human insulin via an amide bond (13). Compared with nonmodified insulin, HIM2 has alterations in physio-chemical characteristics that resist enzymatic degradation and facilitate absorption. In the current study, HIM2 was administered as an oral semisolid formulation in hard gelatin capsules.

Because oral HIM2 is absorbed from the gastrointestinal tract directly into the portal circulation, HIM2 may influence glucose levels primarily by suppressing

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**Abbreviations:** 2pp, 2-h postprandial plasma glucose concentration; 2pp<sub>ex</sub>, 2-h postprandial plasma glucose excursion;  $AUC_{0-240}$ , area under the curve from 0 to 240 min;  $C_{max}$ , maximum concentration;  $G_{ex,max}$ , maximum plasma glucose excursion;  $G_{max}$ , maximum plasma glucose concentration; HIM2, hexyl-insulin monoconjugate 2;  $T_{max}$ , time to maximum concentration.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

hepatic glucose output in a manner similar to that of endogenous insulin in individuals without diabetes. By mimicking the physiological mode of action, insulin therapy with oral HIM2 may provide safe treatment that normalizes metabolic control without producing hyperinsulinemia in the peripheral circulation.

The current study was designed to test the postprandial glucose-lowering effect of a single, oral dose of HIM2 in patients with type 2 diabetes. The effect of HIM2 was compared to the effects of subcutaneous regular insulin and oral placebo in a three-way crossover study design.

## RESEARCH DESIGN AND METHODS

**Subjects.** Patients who participated in the study were men or women; were 36 to 65 years of age; were diagnosed with type 2 diabetes (1); had disease duration of at least 3 years; had fasting blood glucose levels of 125–252 mg/dl; had a HbA<sub>1c</sub> level of 6.8–11.4%; had a BMI of 20.8–37.2 kg/m<sup>2</sup>; were following an appropriate regimen of diet and exercise; were on a stable regimen of oral hypoglycemic drugs but had no prior insulin exposure; and were without a major illness or disability. Daily fasting blood glucose levels were documented by each patient for 5 days preceding the first dose of study drug. Prior oral hypoglycemic drugs were discontinued for at least five half-lives before receiving study drug (metformin therapy was discontinued for at least 5 days).

**Study design.** The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practices. The study protocol and informed consent forms were approved by the Quorum Review IRB (Seattle, WA) and the Human Research Committee Kaleida Health (Buffalo, NY).

In this randomized, placebo- and regular insulin-controlled, three-way crossover, dose-escalation study, patients were randomized to the order in which they received each study drug (oral HIM2, subcutaneous regular insulin, and oral placebo). Patients were blinded to treatment with oral HIM2 and oral placebo; however, patients were not blinded when they received subcutaneous injections of regular insulin (Humulin R). A single dose of each of the following study drugs was administered to each patient on 3

separate days after an overnight fast of at least 8 h: oral HIM2 (at one of three dose levels: 0.375, 0.5, or 1.0 mg/kg), subcutaneous regular insulin (8 units Humulin R), and oral placebo. The 0.375-, 0.5-, and 1.0-mg/kg doses of HIM2 corresponded to ~10.8, 14.4, and 28.7 IU/kg. The dose of 8 IU of subcutaneous regular insulin was estimated, on average, for an 80-kg person based on the insulin dosage algorithm described by Skyler et al. (14).

The time of dosing was assigned as time 0; all other time points on each dosing day are relative to that time. At 30 min after dosing, patients ingested a standardized test meal (16 oz/720 calories/90 g carbohydrate of Boost Plus). The entire amount of Boost Plus was ingested over a 10-min period. Blood samples were collected for determination of plasma glucose and insulin concentrations at 0, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 200, 220, and 240 min after dosing.

A total of nine patients were enrolled at the Diabetes and Glandular Disease Research Clinic (San Antonio, TX), and nine patients were enrolled at the Diabetes-Endocrinology Center of Western New York (Buffalo, NY). A total of six patients (three patients at each study center) were enrolled in each HIM2 dosing group. At each study center, escalations from the 0.375 to the 0.5 and 1.0 mg/kg dose levels were permitted only if the safety and tolerability of HIM2 was confirmed in the previous dosing group.

**Sample collection and assays.** Venous blood samples for determination of plasma glucose and insulin concentrations were drawn into tubes containing ethylenediamine tetraacetic acid at the following time points: 0 (immediately before dosing), 10, 20, 30 (immediately before the meal), 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 200, 220, and 240 min. Samples were gently inverted 8–10 times and centrifuged at 1,300g for 10 min at 4°C. The plasma was separated, frozen within 60 min of collection, and stored at –7°C until assayed. Plasma glucose concentrations were determined using a glucose oxidase-based enzymatic assay (Roche Diagnostics/Boehringer Mannheim Hitachi 911 analyzer), with a lower limit of detection of 2 mg/dl. Plasma insulin concentrations were determined using a radioimmunoassay kit (Linco Research, St. Charles, MO), with a lower limit of detection of 0.07 ng/ml (2

μU/ml). Insulin concentration values less than the lower limit of detection were assigned a value of 0.07 ng/ml (2 μU/ml).

Blood glucose levels were determined on site immediately after collection using a Yellow Springs Instruments glucose analyzer (YSI, Yellow Springs, OH).

**Data analysis.** The following glucodynamic and pharmacokinetic parameters were calculated from the plasma glucose or insulin concentrations after dosing: 2-h postprandial plasma glucose concentration (2pp); maximum plasma glucose concentration ( $G_{max}$ ); area under the plasma glucose concentration time curve from 0 to 240 min (glucose AUC<sub>0–240</sub>); 2-h postprandial plasma glucose excursion (2pp<sub>ex</sub>); maximum plasma glucose excursion ( $G_{ex,max}$ ); area under the plasma glucose excursion time curve from 30 to 240 min (glucose AUC<sub>ex30–240</sub>); maximum plasma insulin concentration (insulin  $C_{max}$ ); time to maximum plasma insulin concentration (insulin  $T_{max}$ ); and area under the insulin concentration time curve from 0 to 240 min (insulin AUC<sub>0–240</sub>).

Plasma glucose excursions were calculated by subtracting the 30-min plasma glucose concentration (start of the meal) from each plasma glucose concentration. The areas under the plasma concentration time curves were calculated using the linear trapezoidal method.

Calculations were performed with SAS version 6.12 (SAS Institute, Cary, NC). Data are expressed as means ± SD in the text and tables; data are expressed as means ± SE in the figure. Wilcoxon's signed-rank test was used to test for statistically significant differences between HIM2 and placebo treatments. The glucodynamic equivalence of HIM2 and subcutaneous insulin was tested by calculating a 95% CI on the mean ratios for the six glucodynamic parameters (2pp,  $G_{max}$ , glucose AUC<sub>0–240</sub>, 2pp<sub>ex</sub>,  $G_{ex,max}$ , and glucose AUC<sub>ex0–240</sub> [log-transformed]) between HIM2 and subcutaneous insulin for each subject. Equivalence testing was performed on pooled data from the 0.5 and 1.0 mg/kg HIM2 dosing groups. Equivalence to within a stringent 10% tolerance was demonstrated if the entire 95% CI fell within the range 0.9–1.1. This is algebraically equivalent to the “two one-tailed tests” method of demonstrating equivalence.

Table 1—Demographic and baseline characteristics of the study patients

	All patients	Group A 0.375 mg/kg	Group B 0.5 mg/kg	Group C 1.0 mg/kg
<i>n</i>	18	6	6	6
Age (years)	54.4 ± 7.3	58.5 ± 5.4	52.2 ± 3.3	52.7 ± 10.6
Weight (kg)	92.2 ± 16.5	85.3 ± 21.0	98.2 ± 12.0	93.3 ± 15.5
BMI (kg/m <sup>2</sup> )	29.7 ± 4.3	28.5 ± 6.3	31.1 ± 2.8	29.5 ± 3.4
Duration of diabetes (years)	6.0 ± 3.9	10.1 ± 4.2	3.8 ± 1.2	4.2 ± 1.7
HbA <sub>1c</sub> (%)	8.6 ± 1.2	8.9 ± 1.1	9.1 ± 1.5	7.9 ± 0.8
C-peptide (ng/ml)	3.8 ± 1.3	3.8 ± 1.7	3.9 ± 1.1	3.7 ± 1.5
Fasting plasma glucose (mg/dl)	171.8 ± 54.6	174.3 ± 40.6	203.2 ± 64.0	137.8 ± 42.8

Data are means ± SD.

## RESULTS

**Demographic and baseline characteristics.** Table 1 presents a summary of the demographic and baseline characteristics of the 18 patients who participated in this study. Patients were either Caucasian (11 patients) or Hispanic (7 patients), with a mean age of 54.4 ± 7.3 years, a mean HbA<sub>1c</sub> level of 8.6 ± 1.2%, and a mean C-peptide level of 3.8 ± 1.3 ng/ml. The most common oral hypoglycemic agents used by patients were glyburide (seven patients), glipizide (seven patients), rosiglitazone (five patients), and metformin (three patients).

Demographic and baseline characteristics were generally similar among dosing groups; however, differences among the three groups were noted in duration of diabetes (based on time since diagnosis), HbA<sub>1c</sub> levels, and fasting plasma glucose levels.

**Safety.** There were no deaths, serious adverse events, or discontinuations due to adverse events in this study. There were no reports of symptomatic hypoglycemia or hyperglycemia. Adverse events were experienced by a total of 13 patients (72.2%). The most common adverse events were headache (six patients, 33.3%) and anemia (three patients, 16.7%). The anemia, evidenced by decreasing hematocrit and decreasing erythrocyte count in these three patients, was most likely due to the multiple blood draws during the course of the study, since these parameters decreased as the study progressed regardless of which study drug the patient was receiving at any given time. The majority of adverse events were determined by the investigator to be mild in intensity and unrelated to study drug. One patient in the 1.0 mg/kg HIM2 dose group experienced mild ad-

verse events of headache, nervousness, and dizziness that were determined by the investigator to be possibly related to study drug; this patient was receiving oral placebo and subcutaneous regular insulin when these events occurred.

**Glucodynamics and pharmacokinetics.** Glucodynamic and pharmacokinetic parameters are summarized for each HIM2 dose group in Table 2. Although there were no consistent differences in glucodynamic parameters between HIM2 and placebo at the lowest dose level (0.375 mg/kg), HIM2 was more effective than placebo at controlling the postprandial rise in plasma glucose concentrations at the 0.5- and 1.0-mg/kg dose levels. This was represented by consistently lower glucodynamic parameter values for HIM2 (0.5 and 1.0 mg/kg) compared with placebo. For example, mean glucose AUC<sub>0–240</sub> and AUC<sub>Cex30–240</sub> were both lower following administration of 0.5 mg/kg HIM2 compared with placebo (1,097.1 vs. 1,196.9 and 256.6 vs. 301.7 mg · h<sup>-1</sup> · dl<sup>-1</sup>, respectively). Similarly, mean glucose AUC<sub>0–240</sub> and AUC<sub>Cex30–240</sub> were both lower following administration of 1.0 mg/kg HIM2 compared with placebo (801.1 vs. 992.1 and 207.6 vs. 262.0 mg · h<sup>-1</sup> · dl<sup>-1</sup>, respectively). The difference in glucose AUC<sub>0–240</sub> between HIM2 and placebo was statistically significant at the 1.0-mg/kg HIM2 dose level (*P* < 0.05 using Wilcoxon's signed-rank test). In addition, several other glucodynamic parameters were statistically significant between HIM2 (0.5 and 1.0 mg/kg) and placebo as indicated in Table 2.

The lowest dose level of HIM2 (0.375 mg/kg) was less effective than 8 units of subcutaneous regular insulin (Humulin-R) at decreasing glucodynamic param-

eters. However, HIM2 at the 0.5- and 1.0-mg/kg dose levels was as effective as 8 units of subcutaneous insulin at controlling postprandial plasma glucose concentrations. This was represented by similar values for HIM2 (0.5 and 1.0 mg/kg) and subcutaneous insulin (8 units) for the majority of glucodynamic parameters. For example, mean glucose AUC<sub>0–240</sub> was similar following the administration of 0.5 mg/kg HIM2 and 8 units of subcutaneous insulin (1,097.1 vs. 1,048.0 mg · h<sup>-1</sup> · dl<sup>-1</sup>). Likewise, mean glucose AUC<sub>0–240</sub> and AUC<sub>Cex30–240</sub> were similar following administration of 1.0 mg/kg HIM2 and 8 units of subcutaneous insulin (801.1 vs. 875.2 and 207.6 vs. 201.2 mg · h<sup>-1</sup> · dl<sup>-1</sup>, respectively).

We next explored the relationship between plasma glucose and plasma insulin concentrations following administration of HIM2, placebo, and subcutaneous insulin. In relation to placebo, HIM2 (0.5 mg/kg) resulted in exposure to peripheral insulin concentrations that were similar to placebo (mean insulin AUC<sub>0–240</sub> 193.1 vs. 196.1 μU · h<sup>-1</sup> · ml<sup>-1</sup>); however, this dose level of HIM2 was associated with a greater decrease in postprandial glucose concentrations compared with placebo (mean glucose AUC<sub>0–240</sub> of 1,097.1 vs. 1,196.9 mg · h<sup>-1</sup> · dl<sup>-1</sup>). In relation to subcutaneous insulin, HIM2 (0.5 and 1.0 mg/kg) resulted in lower peripheral insulin concentrations compared with 8 units subcutaneous regular insulin (mean insulin AUC<sub>0–240</sub> of 193.1 vs. 233.6 and 230.8 vs. 270.3 μU · h<sup>-1</sup> · ml<sup>-1</sup>, respectively); however, these dose levels of HIM2 resulted in comparable control of postprandial plasma glucose concentrations (mean glucose AUC<sub>0–240</sub> of 1,097.1 vs. 1,048.0 and 801.1 vs. 875.2 mg · h<sup>-1</sup> · dl<sup>-1</sup>, respectively).

Table 2—Glucodynamic and pharmacokinetic parameters

	Group A			Group B			Group C			Group B + Group C			
	Oral HIM2 0.375 mg/kg	SQ insulin 8 units	Oral placebo	Oral HIM2 0.5 mg/kg	SQ insulin 8 units	Oral placebo	Oral HIM2 1.0 mg/kg	SQ insulin 8 units	Oral placebo	Oral HIM2 0.5 + 1.0 mg/kg	SQ insulin 8 units	Oral placebo	HIM2/SQ (95% CI)
n	6	6	6	6	6	6	6	6	6	12	12	12	12
2pp (mg/dl)													
Mean	291.7	264.3	304.5	298.7*	298.0	347.3	229.5*	242.3	284.2	264.1†	270.2	315.8	0.97§
SD	46.7	35.9	41.8	54.1	57.6	59.7	49.1	47.6	72.2	61.1	58.2	71.3	(0.90–1.06)
G <sub>max</sub> (mg/dl)													
Mean	303.2	280.7	321.2	314.8*	306.5	361.7	250.8*	261.7	292.0	282.8†	284.1	326.3	0.99§
SD	51.4	43.0	53.4	56.6	66.0	69.1	45.8	36.5	67.3	59.4	56.0	74.5	(0.93–1.06)
Glucose AUC <sub>0–240</sub> (mg · h · dl <sup>-1</sup> )													
Mean	1019.7	967.6	1106.8	1097.1	1048.0	1196.9	801.1*	875.2	992.1	949.1†	961.6	1094.5	0.98§
SD	115.6	112.6	103.4	218.8	218.9	242.9	168.5	149.8	254.7	242.0	200.3	260.3	(0.90–1.06)
2pp <sub>ex</sub> (mg/dl)													
Mean	113.2	67.5	99.3	89.8	76.5	123.0	82.5	74.5	103.0	86.2‡	75.5	113.0	1.12
SD	56.5	57.8	60.5	21.9	30.7	12.3	45.8	23.5	40.7	34.4	26.1	30.5	(0.82–1.53)
G <sub>ex</sub> <sub>max</sub> (mg/dl)													
Mean	124.7	83.8	116.0	106.0*	85.0	137.3	103.8	93.8	110.8	104.9‡	89.4	124.1	1.17
SD	60.1	56.5	70.5	22.4	31.2	16.1	45.3	15.9	35.4	34.1	24.0	29.6	(0.89–1.55)
Glucose AUC <sub>ex</sub> <sub>30–240</sub> (mg · h · dl <sup>-1</sup> )													
Mean	294.7	174.9	279.4	256.6	158.3	301.7	207.6	201.2	262.0	232.1	179.7	281.8	1.40
SD	154.0	150.9	166.6	45.9	90.3	45.1	115.5	55.0	120.4	87.6	74.7	89.1	(0.81–2.44)
Insulin C <sub>max</sub> (μU/ml)													
Mean	66.4	74.2	74.7	72.2	84.5	75.7	149.9	108.4	78.2	111.0	96.3	76.8	—
Median	63.5	77.5	82.5	70.5	82.0	64.0	77.0	77.5	52.0	70.5	82.0	58.4	—
SD	37.0	30.8	42.8	32.8	35.4	39.8	180.1	95.2	58.4	130.0	69.7	47.6	—
Insulin T <sub>max</sub> (h)													
Mean	2.6	2.6	2.6	1.9	2.3	2.8	2.1	2.5	2.4	2.0	2.4	2.6	—
Median	2.8	2.8	2.3	2.1	2.6	2.7	2.3	2.6	2.3	2.2	2.6	2.4	—
SD	1.2	1.1	1.1	1.0	0.6	0.8	1.2	0.8	0.4	1.0	0.7	0.6	—
Insulin AUC <sub>0–240</sub> (μU · h · ml <sup>-1</sup> )													
Mean	169.9	179.7	165.8	193.1	223.6	196.1	230.8	270.3	169.3	212.0	247.0	182.7	—
Median	178.0	179.7	172.4	183.5	221.1	173.6	169.9	198.6	123.9	175.5	218.7	143.5	—
SD	84.8	69.0	86.8	88.3	82.7	102.0	147.2	219.7	106.5	117.4	160.2	100.4	—

Glucose AUC<sub>0–240</sub> = area under the plasma glucose concentration time curve from 0 to 240 minutes; Glucose AUC<sub>ex</sub><sub>30–240</sub> = area under the plasma glucose excursion time curve from 30 to 240 minutes; Insulin C<sub>max</sub> = maximum insulin concentration; Insulin T<sub>max</sub> = time to maximum insulin concentration; Insulin AUC<sub>0–240</sub> = area under the plasma insulin concentration time curve from 0 to 240 min. Statistical significance vs. placebo using the Wilcoxon signed-rank test based on within-patient comparisons. \*P < 0.05, †P = 0.001, ‡P < 0.01. §Equivalent to within 10% by the “two one-sided test” criterion (at P < 0.05).

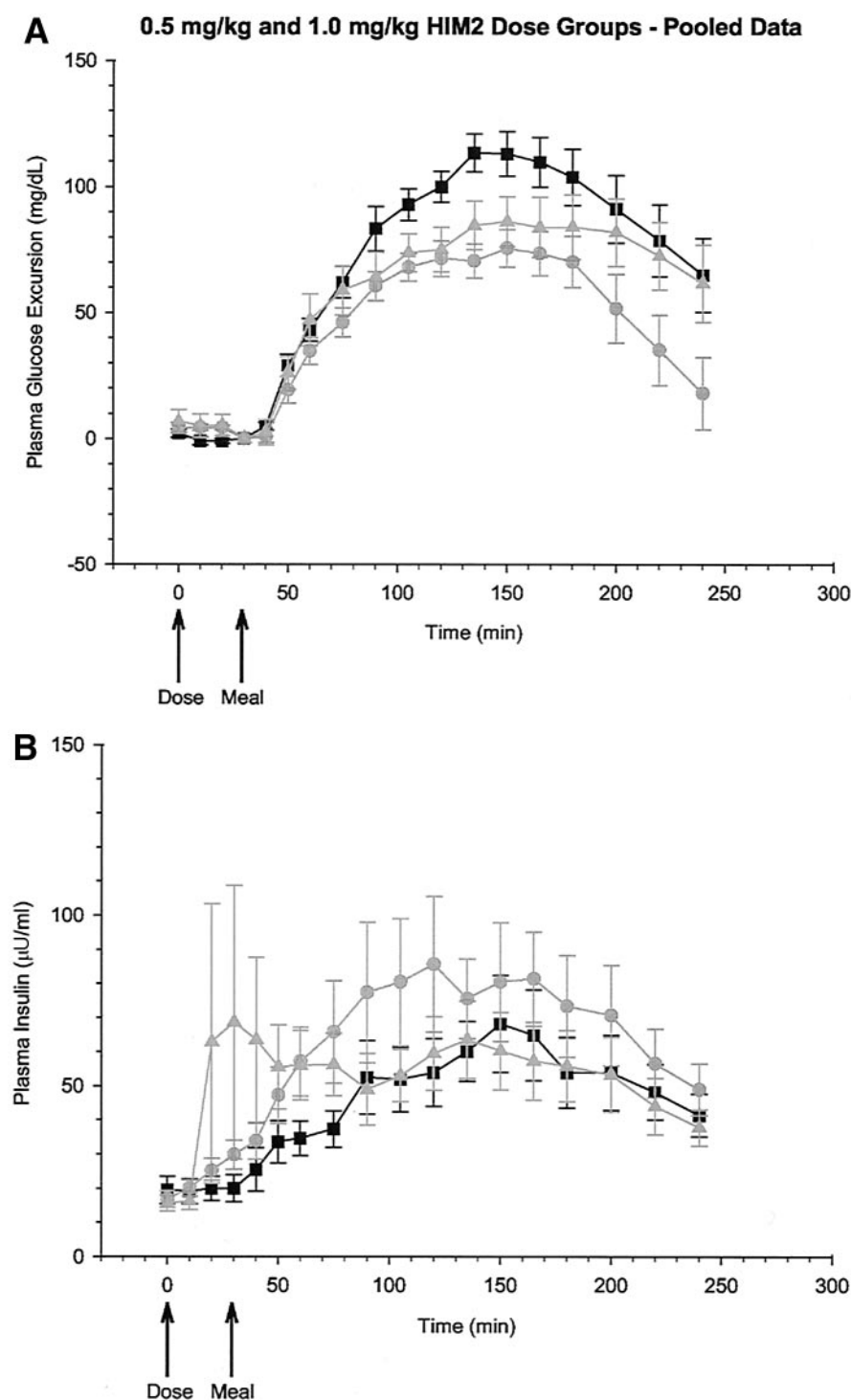
Because the 0.5- and 1.0-mg/kg HIM2 dose levels showed the same general effects on postprandial plasma glucose concentrations, we pooled and analyzed the combined data for these two dose groups. The glucose excursion data for the 0.5- and 1.0-mg/kg pooled data, depicted graphically in Fig. 1, illustrate the similarities and differences among HIM2, subcutaneous insulin, and pla-

cebo. All three curves are indistinguishable from each other during the first hour postdose. The placebo curve then separates from the other two curves, displaying a significantly higher peak excursion. The HIM2 and subcutaneous insulin curves remain nearly indistinguishable for at least another hour. During the fourth hour postdose, the HIM2 curve clearly separates from the subcutaneous

insulin curve, becoming nearly identical to the placebo curve, as the glucose excursion values in all three groups decline toward baseline levels.

The glucodynamic parameters for the 0.5- and 1.0-mg/kg pooled data are summarized in Table 2. The differences in glucodynamic parameters between HIM2 and placebo were statistically significant for the majority of parameters (P < 0.05





**Figure 1**—Mean plasma glucose excursion versus time profiles (A) and mean plasma insulin concentration versus time profiles (B). At time 0, patients received 0.5 or 1.0 mg/kg oral HIM2, 8 units subcutaneous regular insulin, or oral placebo. At 30 min, patients began ingesting the standardized meal (Boost Plus). Patients ingested the entire meal over a 10-min period. Postprandial plasma glucose excursions and insulin concentrations were determined from blood samples collected at the time points indicated. Data are expressed as means  $\pm$  SE ( $n = 12$  patients).  $\blacktriangle$ , oral HIM2 (0.5 and 1.0 mg/kg dose groups combined);  $\bullet$ , 8 units of subcutaneous regular insulin;  $\blacksquare$ , oral placebo.

using Wilcoxon's signed-rank test for  $2pp$ ,  $G_{max}$ ,  $AUC_{0-240}$ ,  $2pp_{ex}$ , and  $Gex_{max}$ ). The results of the test of glucodynamic equivalence, presented in the last column of Table 2, imply that HIM2 and subcutaneous insulin were equivalent (to within 10%) with regard to  $2pp$ ,  $G_{max}$ , and  $AUC_{0-240}$ . However, glucodynamic equivalence was not demonstrated for the excursion parameters ( $2pp_{ex}$ ,  $Gex_{max}$ , and glucose  $AUC_{30-240}$ ).

The peripheral plasma insulin data for the 0.5- and 1.0-mg/kg pooled data, depicted graphically in Fig. 1, revealed an initial peak in peripheral plasma insulin concentrations following administration of HIM2. This initial insulin peak resembled first-phase insulin secretion, which is missing in patients with type 2 diabetes. However, on closer examination, it was observed that this initial insulin peak was due primarily to one patient who had a rapid peak of insulin of 507  $\mu$ U/ml following administration of 1.0 mg/kg HIM2, which is considerably higher than the  $C_{max}$  for all other subjects receiving 0.5 or 1.0 mg/kg HIM2 ( $C_{max}$  range, 30–155  $\mu$ U/ml). The median insulin  $C_{max}$  values, following administration of 1.0 mg/kg HIM2 or 8 units subcutaneous regular insulin, were nearly identical (77.0 vs. 77.5  $\mu$ U/ml, respectively).

**CONCLUSIONS**— In the context of this study, single oral doses of HIM2 were safe and well tolerated in patients with type 2 diabetes. The reported adverse events were predominantly mild, and there were no reports of serious adverse events. Symptomatic events of hyperglycemia or hypoglycemia were not observed during the course of the study.

The goal of this exploratory study was to determine the effectiveness of a single, oral dose of HIM2 in controlling postprandial glycemia in patients with type 2 diabetes. In comparison with placebo treatment, administration of 0.5 and 1.0 mg/kg of HIM2 at 30 min before a meal resulted in lower postprandial plasma glucose levels during a 4-h postdose evaluation period. Statistically significant differences in postprandial plasma glucose parameters between HIM2 and placebo were evident when mean plasma glucose parameters were compared in the 0.5- and 1.0-mg/kg dosing groups and after combining data for these dosing groups.

In comparison with subcutaneous insulin treatment, administration of 0.5 and

1.0 mg/kg of HIM2 at 30 min before a meal resulted in similar postprandial glucose levels during the postdose evaluation period. Equivalence testing demonstrated that HIM2 (0.5- and 1.0-mg/kg pooled data) and subcutaneous insulin (8 units) are equivalent to within 10% with respect to the glucodynamic parameters  $2pp$ ,  $G_{max}$ , and glucose  $AUC_{0-240}$ . We were not surprised, however, to see that the excursion parameters,  $2pp_{ex}$ ,  $G_{ex,max}$ , and glucose  $AUC_{ex,30-240}$ , did not meet the stringent equivalence criteria because the excursion parameters themselves are differences between two quantities, and the ratios of differences are unstable numerically, especially when the magnitudes of the differences are small relative to their variability. The glucose excursion data are consistent with the fact that HIM2 is a rapid-acting form of insulin. HIM2 appears to exert its effects primarily within the first 2–3 h postdose, which is consistent with its intended therapeutic use of controlling postprandial glucose excursion.

The potential benefits of oral delivery of insulin include control of plasma glucose levels without peripheral hyperinsulinemia and restoration of the physiological pathway of endogenous insulin in individuals without diabetes. Delivery of therapeutic levels of insulin via the portal route decreases hyperinsulinemia and may result in preservation of the counter-regulatory responses to hypoglycemia, with concomitant reduction in hypoglycemic events (15–17). An important observation from the current study was that oral HIM2 at doses of 0.5 and 1.0 mg/kg, in comparison with 8 units of subcutaneous regular insulin, provided comparable postprandial glucose control at lower peripheral insulin concentrations. These data are consistent with the hypothesis that oral delivery of insulin may lead to the development of a portal-to-peripheral insulin gradient similar to the state observed in individuals not given subcutaneous insulin. These data also suggest that a reduced risk of hypoglycemia, compared with subcutaneous insulin therapy, can reasonably be expected in patients who receive oral HIM2 therapy.

The results of this study suggest that oral HIM2 may be useful in patients with type 2 diabetes who experience inadequate postprandial glycemic control.

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