Long-Term Use of Intranasal Insulin in Insulin-Dependent Diabetic Patients

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This study, in 3 phases, compared the long-term acceptability and efficacy of insulin administered by nasal spray with an intensified subcutaneous regimen in nine type I (insulin-dependent) diabetic subjects on baseline therapy with ultralente insulin. In phase 1, patients were begun and stabilized on a regimen of ultralente daily and Actrapid insulin three times daily. Phase 2 consisted of 4 mo of this intensified subcutaneous regimen. In phase 3, intranasal administration of insulin, with 1% (wt/vol) sodium glycocholate, replaced Actrapid insulin for 4 mo. Glycemic control was compared in each of the three phases. It was possible to maintain the dose of ultralente insulin relatively constant in only six of the nine subjects during the intranasal phase of the study. The six subjects showed a significant rise in glycosylated hemoglobin during the intranasal phase (10.4 ± 0.6% intranasal vs. 9.1 ± 0.3% subcutaneous, $P < .05$) but not in plasma or urinary glucose levels. There was no significant change in the incidence of hypoglycemic episodes during intranasal insulin therapy in this group. The other three subjects were considered treatment failures. Six of the nine original subjects expressed a preference for intranasal insulin, and one subject complained of mild nasal irritation insufficient to cease treatment. The intranasal route of administration of insulin has the potential to replace short-acting insulin as an adjunct to longer-acting insulin in some insulin-treated diabetic patients. *Diabetes Care* 10:573–78, 1987

Intranasal insulin lowers fasting plasma glucose levels (1–6) and reduces postprandial hyperglycemia (6–9). Serum insulin levels rise rapidly with a short plasma half-life, resembling intravenous rather than subcutaneous injections of insulin (4). The bioavailability of intranasal compared with subcutaneous insulin is ~12% (6). We have previously shown that, although single doses of intranasal insulin reduced postrandial hyperglycemia in type II (non-insulin-dependent) diabetic subjects, better glycemic control was achieved with two or three doses given at 30-min intervals, with the first dose given at the start of the meal (6). We have used a modified version of this regimen in this clinical study of the efficacy of intranasal insulin in type I (insulin-dependent) diabetic patients.

The role of intranasal insulin in the long-term treatment of diabetes has received little attention and has been the subject of only one report, which examined the combined effects of subcutaneous and intranasal insulin on diabetic control (10). The dosage and type of long-acting subcutaneous insulin varied considerably in that study and therefore did not clearly separate the effects of intranasal insulin from those of the concurrently administered long-acting subcutaneous insulin. We avoid this problem by maintaining the dosage of long-acting (ultralente) insulin within constant limits during both the intranasal and subcutaneous phases of the study (11).

SUBJECTS AND METHODS

Subjects. Subjects considered for inclusion in this study were type I diabetic individuals, 15–60 yr old, who were long-term attenders of the Endocrine Clinic at the Austin Hospital. All gave informed consent before entering the study. All subjects monitored capillary blood glucose levels at least four times daily, and glycosylated hemoglobin (HbA_1) levels measured over the preceding 12 mo did not exceed 12% (normal range 5–8%). Subjects with nasal disease or those receiving other drugs by the intranasal route were excluded.

Patients with progressive diabetic retinopathy and renal impairment (serum creatinine >0.2 mM) were not included in the study.

Insulin preparation. Each subject used a hand-held, metered, nonpressurized aerosol device (Pfeiffer pump, Boehringer, Ingelheim, FRG) that delivered 15 U (60 μl) insulin/spray. The formulation was prepared from crystals of monocomponent porcine insulin (Novo, Copenhagen) to a final concentration of 250 U/ml, together with 1% (wt/vol) sodium glycocholate and 0.14 M phosphate buffer, pH 7.0. Methyl *p*-hydroxybenzoate (0.1% wt/vol) was used as a preservative. Stability studies demonstrated that there was no statistically significant loss of insulin immunoreactivity with storage at 4°C for up to 2 mo. After 6 mo, there was a 10–20% loss. Insulin solutions for patient use were prepared monthly and discarded after 2 mo.

Study protocol. The study protocol is shown in Table 1. The aim of this study was to maintain the dosage of ultralente insulin throughout phases 2 and 3 within 20% of the phase 1 dosage. Inability to achieve this was considered a treatment failure. All subjects were initially stabilized for 2 mo on a regimen of a single dose of ultralente and subcutaneous Actrapid insulin (Novo) three times daily (phase 1). These patients then continued for 4 mo on their stabilized dosage of ultralente and subcutaneous Actrapid insulin three times daily (phase 2). In phase 3, intranasal insulin replaced the subcutaneous Actrapid insulin, and up to 3 divided doses, each of up to 120 U, were given at 30-min intervals at each of the three main meals. All patients received dietary advice at the beginning of the study, and attempts were made to standardize the meals and the meal times during the study. Fasting plasma glucose was taken at 0800 h on monthly study days, and breakfast was consumed at 0830 h. The 1100 h plasma glucose measurement was taken just before a morning snack, and lunch was consumed at 1230 h. Patients were advised to consume their evening meal between 1700 and 1800 h.

Initial pharmacokinetic studies were performed in five of the subjects before entry into the trial. These subjects were given a standardized meal (6) after an overnight fast. At the start of the meal, 30 U intranasal insulin was administered. On a separate study day, 6 U subcutaneous Actrapid insulin was given. Plasma glucose was estimated at regular intervals over 5 h.

TABLE 1
Study protocol

Insulin type	Phase 1 (2 mo)	Phase 2 (s.c., 4 mo)	Phase 3 (intranasal, 4 mo)
Ultralente	+	+	+
Actrapid (s.c., 3 times daily)	+	+	–
Intranasal spray	–	–	+

Glycemic measures. Indices of glycemic control included stable HbA_1 (measured by column chromatography; 12), plasma glucose profiles (fasting, 1100 h, and 1500 h), and 24-h urinary glucose excretion, which were measured monthly. Plasma glucose levels were estimated with the glucose oxidase technique with a centrifugal analyzer (13). Fasting serum C-peptide levels were determined by radioimmunoassay with reagents supplied by Novo. Free-insulin levels were measured by radioimmunoassay (reagents supplied by Wellcome, Beckenham, UK) after polyethylene glycol precipitation of serum (14). The incidence of hypoglycemic episodes and nasal irritation was recorded, and patients were reviewed initially at weekly and then at monthly clinic visits. Hypoglycemia was defined as appropriate symptoms coinciding with capillary blood glucose levels <3 mM.

Algorithms for subcutaneous insulin dosage. All patients were converted from their prestudy insulin regimen to Actrapid insulin three times daily and ultralente insulin once daily (Table 2). The initial doses were equivalent to the total prestudy subcutaneous doses; the ultralente dose composed no more than 50% of the total, and the remainder was of Actrapid divided into three equal doses. The patients were stabilized in this period (phase 1) for 2 mo and then further studied for 4 mo on the stabilized dose (phase 2). During phase 2 the doses of subcutaneous insulin were altered on the basis of patterns of capillary blood glucose levels measured four times daily (at 0700, 1100, 1600, and 2100 h) and recorded. If the 0700 h capillary blood glucose exceeded 10 mM, the dose of ultralente insulin was increased by 2–4 U. If the 1100 h reading exceeded 10 mM, the breakfast dose of Actrapid was increased by 2–4 U. Similar adjustments for midday and evening doses were based on the 1600 and 2100 h capillary blood glucose readings. Analogous reductions in insulin dosage were made on the same basis if capillary blood glucose levels were <4 mM.

Algorithms for intranasal insulin dose. When converting patients from Actrapid to intranasal insulin (phase 3), patients were initially given five times the daily dose of Actrapid insulin used in phase 2 calculated to the nearest multiple of 15 U (i.e., amount delivered by 1 spray). This total daily dose was divided into three equal doses, each given initially as a single dose at the beginning of one of the three main meals. The initial adjustment of the intranasal insulin dose involved increasing the dose at the beginning of the meal until it reached a maximum of 120 U (8 sprays). At higher doses, patients noted that insulin solution was lost from the nose. Because of this, if adequate glycemic control was not achieved with doses of 120 U, a second dose of intranasal insulin was given 30 min after the first. If further dose increases were necessary, the second dose was progressively increased to a maximum of 120 U, and a further dose was administered 30 min later when necessary. No patient required >3 doses of 120 U in association with a meal. The period of dosage adjustment ranged from 7 to 21 days. The doses of intranasal insulin were altered, like subcutaneous insulin, on the basis of capillary blood glucose levels measured

TABLE 2
Insulin doses

Subject	Sex	Age (yr)	Duration of diabetes (yr)	Fasting C-peptide (pmol/ml)	Prestudy treatment	Ultralente dose at end of phase 2 and phase 3 (U)		Subcutaneous dose (A) at end of phase 2 (U)			Intranasal dose at end of phase 3 (U)		
						Phase 2	Phase 3	Morning	Noon	Evening	Morning	Noon	Evening
1	M	34	10	0.01	A/M twice daily	44	50	2	6	14	90	90	90
2*	M	21	3	0.01	A/M twice daily	26	60	20	6	10	330	240	180
3*	M	48	34	0.01	A/M twice daily	22	36	10	5	9	270	270	240
4	M	22	9	0.01	A/M twice daily	52	58	18	12	10	360	360	360
5*	M	17	4	0.02	A/M twice daily	36	64	25	5	11	360	330	360
6	F	51	1	0.06	R/NPH daily	10	10	4	4	4	150	120	150
7	M	59	10	0.04	R/NPH daily	18	18	8	4	8	135	135	135
8	M	43	6	0.02	A/M twice daily	24	28	8	6	8	60	60	60
9	M	37	21	0.01	R/NPH twice daily	40	42	14	2	10	270	135	210

A, Actrapid; M, Monotard; R, regular insulin; NPH, Isophane. Normal range for fasting C-peptide: 0.18–0.63 pmol/ml.
*Excluded from statistical analysis because ultralente dose increased by >20% during phase 3.

four times daily. During the initial stabilization period, patients were reviewed every 24 h, usually by telephone. If the 0700 h capillary blood glucose exceeded 10 mM, the dose of ultralente insulin was increased by 2–4 U. If the 1100 h reading exceeded 10 mM, the breakfast dose of intranasal insulin was increased by 15–30 U (1–2 sprays). Similar adjustments for midday and evening doses were based on the 1600 and 2100 h readings, and analogous reductions in insulin dose were made if levels were <4 mM.

Statistical analysis. Statistics were performed by paired and unpaired Student's *t* tests and by the Mann-Whitney test for data that were not normally distributed (24-h urinary glucose). The parameters analyzed were plasma glucose profiles, HbA_1, and 24-h urinary glucose excretion.

The analyses were performed with and without three subjects who required an increase >20% in the dose of ultralente insulin during phase 3 of the study. The periods were compared as follows: phase 1, last 2 mo of phase 2, and last 2 mo of phase 3. Comparisons of glycemic control between different treatment phases in the same subject were performed by paired *t* tests. Comparison of the glycemic profiles over 5 h in the pharmacokinetic studies was performed by two-way analysis of variance (15).

RESULTS

The clinical characteristics and doses of subcutaneous and intranasal insulin are shown in Table 2. Patients 2, 3, and 5 required a substantial increase in their doses of ultralente insulin during phase 3 of the study because of fasting hyperglycemia and were considered to be treatment failures. At entry, glycemic control and fasting C-peptide levels in these three subjects were not significantly different from corresponding values in the other six subjects ($P = .5$ for HbA_1; $P = .9$, .6, and .1 for 0800, 1100, and 1500 h glucose levels, respectively; $P = .6$ for C-peptide). However, fasting plasma glucose levels were significantly greater at the end of phase 3 in the three "failed" subjects ($P < .02$). At the end of phases 2 and 3, other measures of glycemic control (HbA_1, postrandial plasma glucose, and urinary glucose levels) were

TABLE 3
Glycemic control in subjects ($n = 3$) in whom the dosage of ultralente insulin increased by >20% (subjects 2, 3, and 5 in Table 2)

	At entry	End of phase 1	End of phase 2 (s.c.)	End of phase 3 (intranasal)
Fasting plasma glucose (mM)	15.6 ± 2.5	14.6 ± 1.5	9.8 ± 2.7	15.6 ± 1.1*
1100 h glucose (mM)	19.2 ± 5.2	11.0 ± 4.4	15.5 ± 3.6	13.6 ± 5.7
1500 h glucose (mM)	11.3 ± 1.0	6.2 ± 0.7	6.0 ± 2.8	18.5 ± 8.5
24-h urinary glucose (mmol/day)	329 (25–941)	229 (8–440)	160 (5–174)	483 (7–662)
HbA_1 (%)	9.0 ± 0.5	9.5 ± 0.6	8.3 ± 0.4	11.0 ± 1.3

Results are means ± SE except for 24-h urinary glucose (range in parentheses).
*$P < .02$ vs. values from 6 subjects in Table 4.

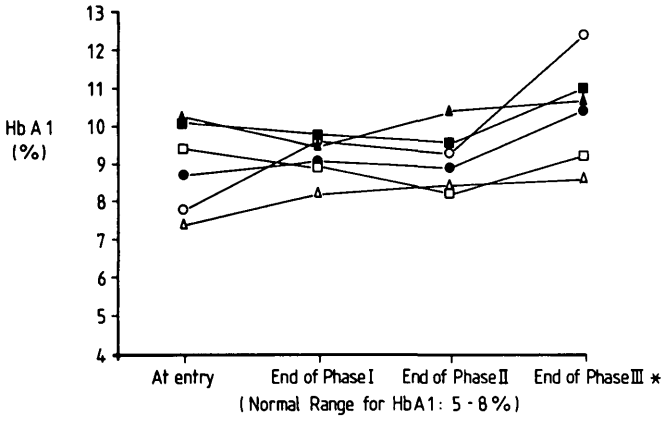

FIG. 1. Individual values of HbA_1 at entry into study, end of phase 1, end of phase 2, and end of phase 3. *$P < .05$ compared with end of phase 2.

not significantly different in the three failed subjects compared with the other six subjects (Table 3).

In the other six patients, there was no significant difference in the dose of ultralente insulin between phases 2 and 3 of the study (31.3 ± 6.7 vs. 34.3 ± 7.7 U/day, $P = .8$). Fasting C-peptide levels were below the normal range in all six subjects, and total daily doses of intranasal insulin varied from 180 to 1080 U, compared to doses of subcutaneous Actrapid insulin, which varied from 12 to 40 U in phase 2 of the study. On average, patients required 21 ± 4 times more insulin when it was administered by the intranasal route. In the acute studies of postprandial glycemic excursion in five of the patients, plasma glucose rose from a baseline of 10.3 ± 1.9 to 15.4 ± 1.8 mM 80 min after a dose of 30 U intranasal insulin. After 6 U s.c. Actrapid insulin with the meal, plasma glucose rose from 10.7 ± 1.2 to 16.1 ± 1.6 mM at 70 min. The postprandial glycemic excursion after intranasal insulin was not statistically different from that seen after subcutaneous insulin over 5 h ($F = 0.04$, NS, two-way analysis of variance). Serum free-insulin levels were estimated in two of the subjects and rose from a baseline of <10 to ~100 μU/ml 10 min after 30 U intranasal insulin. Insulin levels rose to 250–350 μU/ml 10 min after 60 U intranasal insulin. All insulin levels returned to baseline 60 min after intranasal insulin.

Mean levels of HbA_1 are shown in Fig. 1. The HbA_1 level remained <12% in five of the six subjects, <11% in four subjects, and <10% in two subjects during the intranasal phase of treatment. Mean HbA_1 rose significantly from 9.1 ± 0.3 to 10.4 ± 0.6% during intranasal insulin therapy ($P < .05$). The HbA_1, serial plasma glucose, and 24-h urinary glucose levels in all phases of the study are shown in Table 4. There were no significant differences in serial plasma glucose levels during subcutaneous insulin therapy compared with intranasal insulin therapy. Twenty-four-hour urinary glucose excretion did not vary significantly in any phase of the study (phase 2 vs. phase 3, $P = .13$, Mann-Whitney). The number of hypoglycemic episodes per subject per month was similar in phases 2 and 3 of the study (0.8 ± 0.3 vs. 0.5 ± 0.3 episodes per subject per month, $P = .2$).

Six of the nine original subjects expressed a preference for intranasal insulin. Only one subject complained of nasal irritation, but this was not severe enough to cease treatment. Three subjects suffered mild upper respiratory tract infections while using intranasal insulin. One subject developed hyperglycemia in association with the upper respiratory tract infection, but this resolved after 4 days.

DISCUSSION

This study compares the relative value of subcutaneous and intranasal insulin in treating type I diabetic patients. Overall, the intranasal regimen was less effective than an intensified subcutaneous regimen, as judged by HbA_1 and the large increases in insulin dosage requirement. However, more than half of the patients preferred the intranasal route.

Only one previous study examined the use of intranasal insulin on a long-term basis (10). In that study, eight subjects were treated for 3 mo with intranasal insulin, followed by subcutaneous insulin for 3 mo. It was concluded that HbA_1 levels were not significantly altered compared with subcu-

TABLE 4
Glycemic control in subjects ($n = 6$) in whom the dosage of ultralente insulin did not vary by >20% in phases 2 and 3

	At entry	End of phase 1	End of phase 2 (s.c.)	End of phase 3 (intranasal)
Fasting plasma glucose (mM)	13.7 ± 0.7	10.1 ± 1.6	9.6 ± 1.9	10.2 ± 1.0*
1100 h glucose (mM)	16.0 ± 1.2	12.9 ± 2.4	12.1 ± 2.7	11.6 ± 2.2
1500 h glucose (mM)	7.2 ± 1.8	9.0 ± 1.9	7.2 ± 1.2	10.5 ± 2.7
24-h urinary glucose (mmol/day)	120 (29–292)	53 (1–131)	28 (11–182)	159 (13–701)
HbA_1 (%)	9.1 ± 0.3	9.2 ± 0.2	9.1 ± 0.3	10.4 ± 0.6†

Results are means ± SE except for 24-h urinary glucose (range in parentheses).
*$P < .05$ vs. prestudy values.
†$P < .05$ vs. phase 2.

taneous insulin treatment one, two, or three times daily. However, seven of the eight subjects showed an improvement in HbA_1 levels after reverting from intranasal to conventional subcutaneous insulin therapy (10). The specific contribution of intranasal insulin to metabolic control in that study was difficult to assess because there were significant increases of 24, 26, and 48 U in the daily dose of subcutaneously administered long-acting insulin during intranasal insulin therapy in three of the subjects. Moreover, the frequency of administration and type of insulin varied in the subcutaneous phase of the study, and doses used in the intranasal phase were up to 75 times higher than doses used in the subcutaneous phase of that study (10).

Glycemic control, as assessed by HbA_1 levels during the intranasal phase of this study, was worse than with intensified subcutaneous therapy (Fig. 1) but was similar to levels often accepted in clinical practice. The analysis of postprandial plasma glucose levels (1100 and 1500 h) revealed no significant differences between intranasal and subcutaneous insulin therapy (Table 4). Acute studies of postprandial glucose excursion showed similar patterns after intranasal and subcutaneous insulin, with changes in serum insulin levels comparable with those seen in type II diabetic patients (6). However, the doses of intranasal insulin used in this study were on average 21 times higher than their subcutaneous equivalents. This increase in insulin requirement occurred soon after entry to phase 3 and, therefore, was unlikely to be due to any loss of efficacy of the ultralente insulin and reflected the relatively poor bioavailability of intranasal insulin. The expense of these large doses of insulin and the unknown long-term local effects of high insulin concentrations are negative features of intranasal insulin therapy.

Because of difficulties in administering large volumes via the intranasal route and the rapid absorption and short half-life of insulin given in this way, serial doses of intranasal insulin at 30-min intervals were used to control postprandial hyperglycemia in this study. This regimen has been shown to exert additive effects in type II diabetic patients (6). In the future, the use of different surfactants may improve the bioavailability and prolong the action of insulin given intranasally (16,17) and reduce the necessity for multiple doses with a meal. However, it is important to determine the long-term safety of the adjuvant as well as that of the insulin. The use of a nonionic detergent, laureth 9, has been associated with a much higher incidence of nasal irritation and withdrawal from therapy (10) and in animal studies appears to be more damaging to the nasal mucosa than bile salts (18). In our experience with glycocholate as the adjuvant, it did not result in significant nasal side effects in any of the subjects studied.

It is significant that intranasal insulin has reproducibility of absorption comparable with that of subcutaneous insulin. In a previous study in type II diabetic patients, we found that the intersubject coefficient of variation in peak serum insulin levels was 41% for intranasal insulin and 44% for subcutaneous insulin in the fasting state. Within the same subject, serial doses of intranasal insulin when given with meals showed a mean coefficient of variation of 55% (6).

Our data suggest that intranasal insulin satisfactorily controlled blood glucose levels in approximately half the subjects studied. Intranasal insulin has the potential to replace short-acting subcutaneous insulin in some type I patients. Further developments in the clinical use of intranasal insulin will require new adjuvants and methods for improving the bioavailability and duration of action of insulin given via this route of administration.

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