

Insulin Administered Intranasally as an Insulin-Bile Salt Aerosol

Effectiveness and Reproducibility in Normal and Diabetic Subjects

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SUMMARY

Efficacy and reproducibility of insulin administered intranasally as an insulin-deoxycholate 1% (w/v) aerosol to normal and diabetic subjects were assessed by measurements of blood glucose and serum insulin levels. Following administration of 0.5 U insulin/kg with the unconjugated bile salt to fasting volunteers (N = 29), peak serum insulin levels of $103 \pm 49 \mu\text{U/ml}$ above baseline were observed at 10 min. Blood glucose concentration began to fall by 10 min, reaching $54 \pm 14\%$ of control levels by 30 min, and returning to baseline by 60–80 min. Blood glucose response and peak serum insulin levels were reproducible when the same aerosol dose was repeatedly administered to the same subjects; however, intersubject variations were noted. By comparing serum insulin levels after i.v. and nasal routes of administration, nasal insulin absorption was approximately 10% as efficient as intravenous insulin. Dose response studies revealed that peak serum insulin concentrations were a linear function of the administered dose. In subjects with type I and type II diabetes mellitus, serum insulin levels increased in a manner similar to controls, and resulted in a prompt reduction of blood glucose concentration. However, in contrast to normal subjects, the duration of the glucose response was more prolonged, lasting as long as 5 h. Nasal administration of insulin as an aerosol with bile salts or bile salt analogs should be further evaluated as a possible nonparenteral approach to insulin therapy. DIABETES 32:1040–1047, November 1983.

Treatment of diabetic patients with insulin requires parenteral injections. Although lifesaving in type I diabetics and necessary for metabolic control in many type II diabetics, hypodermic injection of insulin is not an ideal means for insulin delivery. Local discomfort and perceived disruption of normal lifestyle deter many type I patients from accepting intensive insulin treatment regimens. Furthermore, many type II diabetics refuse

insulin therapy entirely because of their unwillingness to accept the physical and social trauma involved with insulin injections. For these reasons, investigators have repeatedly attempted to administer insulin by alternate, nonparenteral routes. Insulin has been administered enterally, with and without liposome encapsulation,^{1,2} rectally,³ vaginally,⁴ and through the respiratory epithelium.⁵ Due to limited and variable absorption of insulin, these attempts have met with minimal enthusiasm.

Another possible and poorly explored means of insulin delivery is via the nasal mucosa. Vasopressin,⁶ luteinizing hormone releasing hormone (LHRH),⁷ and an adrenocorticotrophic hormone (ACTH) analog⁸ can be successfully administered by this route, and attempts to similarly administer insulin date back to at least 1958.⁹ More recently, Hirai et al.¹⁰ and Pontiroli et al.¹¹ have demonstrated that insulin mixed with solutions of bile salts and other "surface active" agents crossed the nasal mucosa and caused an increase in serum insulin levels sufficient to lower blood glucose concentrations. However, because of doubts regarding the efficiency and reproducibility of nasal insulin absorption, little attention has been focused on these reports. We have readdressed this issue, and herein report that insulin, when mixed with an appropriate bile salt, can be introduced into the bloodstream by the nasal route with reproducible kinetics and good efficiency. We suggest that this route and means of insulin delivery require further evaluation as an approach to the treatment of diabetes.

MATERIALS AND METHODS

Commercially available U-500 regular porcine insulin was obtained from Eli Lilly and Company (Indianapolis, Indiana).

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TABLE 1
Clinical characteristics of subjects with type I and type II diabetes mellitus

Subject*	Age (yr)	Weight (% ideal)	Duration of diabetes (yr)	Treatment†	Anti-insulin antibodies‡
Type II					
14	56	200	15	Diet alone	0.14
19	55	150	4	Diet and tolazimide	0.03
Type I					
9	28	100	17.5	Insulin (qd) Lente 42 U	0.34
				a.m. Reg. 18 U Lente 8 U	
				p.m. Reg. 18 U NPH 22 U	
12	22	100	17	a.m. Reg. 3 U NPH 22 U	0.16
				p.m. Reg. 3 NPH 23 U Reg. 1 U	
13	30	100	5.5	a.m. NPH 4 U NPH 20 U	0.16
15	30	120	11	p.m. Reg. 10 U NPH 8 U	0.19

*Subjects were assigned numbers at entry into the study. Results from all subjects studied are not included in this table.

†In subject 19, tolazimide was withheld 4 days prior to study. All insulin dosages were administered subcutaneously and were the patients' routine dosages at the time of the study.

‡Anti-insulin antibodies are expressed as ^{125}I -insulin bound by serum divided by free ^{125}I -insulin (B/F) in a charcoal binding assay as described previously.¹⁴ The normal range in this laboratory is B/F < 0.15.

A highly purified bile salt, sodium deoxycholate was obtained from Calbiochem (San Diego, California). Sodium deoxycholate was documented to be greater than 99% pure by high performance liquid chromatography.¹² Serum glucose and whole blood glucose were measured in duplicate on a Yellow Springs glucose analyzer (YS23A). In a few subjects in whom serum glucose was measured, whole blood glucose levels were calculated according to the formula: serum glucose = whole blood glucose divided by 1.106.

Serum immunoreactive insulin levels were determined by antibody coated tube radioimmunoassay kits provided by Clinical Assays, Division of Baxter-Travenol (Cambridge, Massachusetts), according to the specifications of the manufacturer. Serum free insulin levels in diabetic subjects previously treated with insulin were measured following polyethylene glycol precipitation of stored serum samples to remove anti-insulin immunoglobulin.¹³

Twenty-four control subjects, four subjects with type I diabetes mellitus, and two subjects with type II diabetes mellitus were studied (Table 1). Control subjects were within $\pm 15\%$ of ideal body weight, had no history of glucose intolerance, and were free of renal, hepatic, cardiac, and neurologic disease. Fasting blood glucose in the normal subjects was 81 ± 11 mg/dl. Several subjects were studied more than once. All subjects gave informed consent to a protocol approved by the Clinical Investigation Committee of the Beth Israel Hospital and were studied in the morning following an overnight fast. An intravenous catheter for blood

sampling was placed in a forearm vein and patency was maintained by the infusion of 0.9% saline at 15 ml/h. The diagnosis of type I diabetes mellitus was based on the absolute need for parenteral insulin therapy to prevent ketoacidosis. On the day prior to study, the morning dose of intermediate-acting insulin and the evening dose of regular insulin were administered, but the evening dose of intermediate-acting insulin was withheld. No subcutaneous insulin was administered on the morning of the study. During the course of study, all subjects were recumbent, and were allowed free access to water. Type II diabetic subjects had not previously been treated with insulin, and oral hypoglycemic agents were withdrawn 4 days prior to study.

Insulin was administered into each nostril by one of the investigators as a fixed volume aerosol spray [75 ± 8 (mean ± 1 SD) μl per spray]. The volume of liquid dispensed by the spray device was determined gravimetrically by taking the average \pm SD weights of 10 tared tubes into which distilled water was dispensed by the device. The spray device was checked weekly for the accuracy of volume delivered. U-500 insulin was diluted to an appropriate concentration with a solution of sodium deoxycholate (pH 7.6, NaCl 0.15 M) to give a final concentration of deoxycholate of 1% (w/v). The concentration of insulin in the device was varied so as to deliver a dosage of 0.5 U/kg body weight in a total of two sprays unless otherwise stated. Venous blood was drawn at the indicated times, allowed to clot for 30 min at room temperature, and centrifuged at $1,500 \times g$ for 10 min.

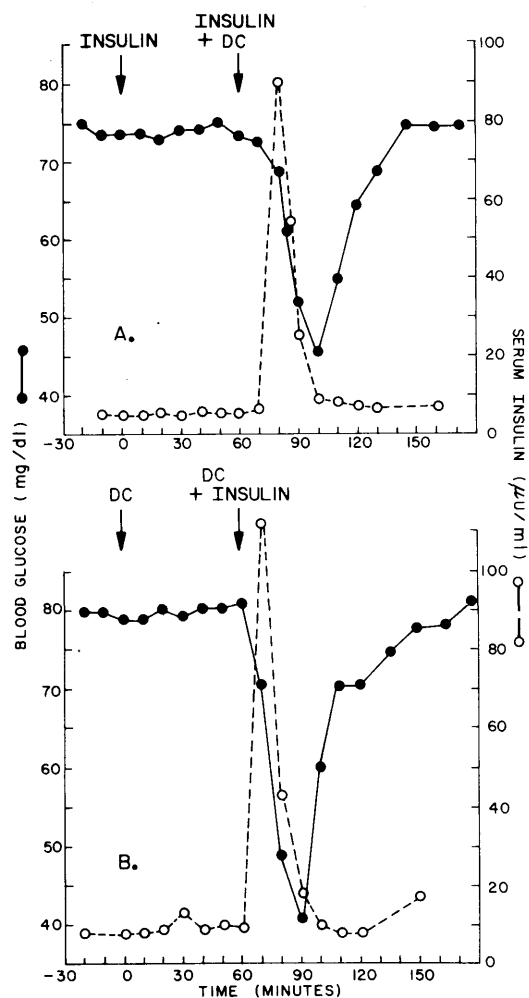


FIGURE 1. Upper panel: Serum insulin (○---○) and blood glucose (●—●) concentrations in a normal volunteer following intranasal aerosol administration of 0.5 U insulin/kg alone (arrow), and 0.5 U insulin/kg with 1% (w/v) deoxycholate (DC, arrow). Lower panel: Serum insulin (○---○) and blood glucose (●—●) concentrations in a normal volunteer following intranasal aerosol administration of 1% deoxycholate (DC, arrow) and 0.5 U insulin/kg with 1% deoxycholate.

Serum was divided into several aliquots and a sample stored at -20°C prior to measurement of immunoreactive insulin. Blood glucose was measured on heparinized blood samples kept on ice prior to measurement. Anti-insulin antibodies were measured as previously described.¹⁴

Statistical analyses were performed using the Analyzer system for a Hewlett-Packard 9854B in the Core Statistics Laboratory of the Beth Israel Hospital. All data are expressed as the mean \pm 1 SD. The area under the serum insulin curve obtained for 60 min following insulin administration was calculated by the trapezoidal rule.

RESULTS

When insulin was administered alone in phosphate-buffered saline, pH 7.4, at a dose of 0.5 U/kg to a volunteer, there was neither a decrease in blood glucose concentration, nor an increase in plasma insulin levels (Figure 1A). When the same dose of insulin (0.5 U/kg) was administered with sodium deoxycholate at a final concentration of 1% (w/v), the blood glucose concentration fell promptly between 10 and

20 min as shown in Figure 1A. Following insulin administration, the nadir of blood glucose occurred at 30 min, and complete recovery was seen by 60–80 min. Serum insulin levels were highest at the first sampling point (10 min after administration) and fell to baseline by 40 min.

To evaluate the remote possibility that nasal deoxycholate might itself produce hypoglycemia, another subject received 1% deoxycholate alone by nasal spray (Figure 1B). Deoxycholate produced no increase in plasma insulin concentrations and no decrease in blood glucose. When the same subject received 0.5 U/kg of regular insulin in 1% deoxycholate, there was a prompt increase in serum insulin concentration followed by a reduction in the blood glucose level (Figure 1B).

To establish the reproducibility of the response to the intranasal administration of insulin, 29 normal volunteers were tested under identical conditions. At time 0, all subjects received 0.5 U/kg of regular insulin in a solution of 1% deoxycholate. To normalize slight differences in fasting blood

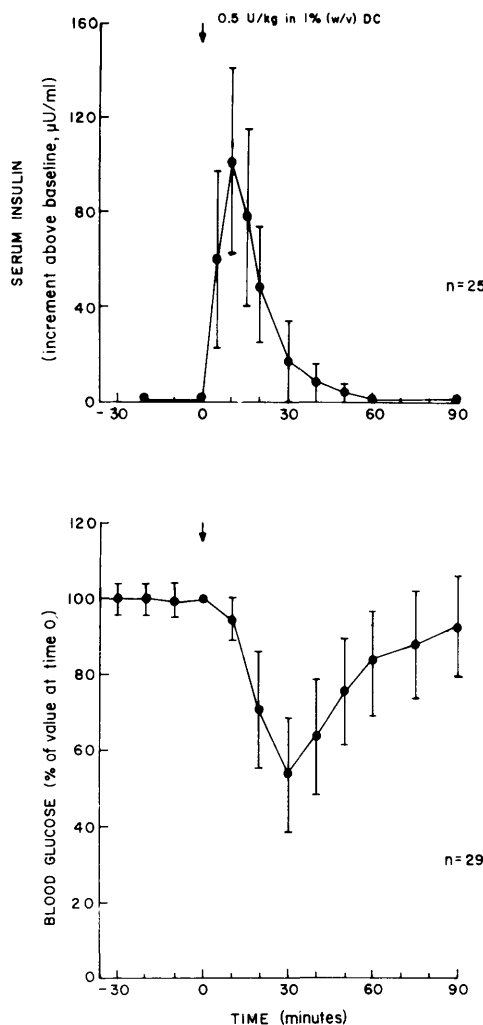


FIGURE 2. Upper panel: Serum insulin levels (mean \pm 1 SD) for 25 normal subjects who received a nasal spray of 0.5 U insulin/kg in 1% (w/v) deoxycholate at time 0. Lower panel: Blood glucose as percentage of the value at time 0 (mean \pm 1 SD) versus time for 29 normal subjects who received 0.5 U insulin/kg-1% (w/v) deoxycholate aerosol at time 0.

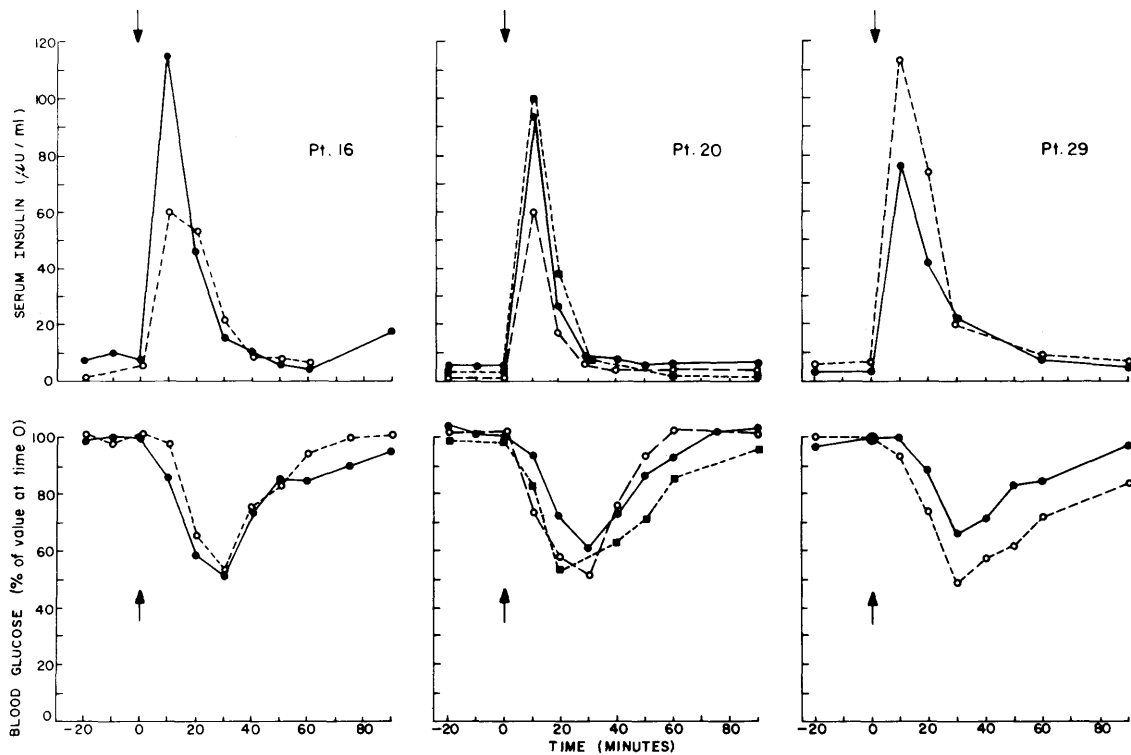


FIGURE 3. Serum insulin levels (upper panel) and change in blood glucose (lower panel) concentrations for three subjects who received repeated administration (>24 h apart) of 0.5 U insulin/kg body weight in 1% (w/v) deoxycholate as a nasal aerosol. Insulin was administered at the time indicated by the arrows.

glucose levels between subjects, the results of these experiments (Figure 2) are expressed as a percentage of initial blood glucose concentrations. The decline in blood glucose began as early as 10 min following intranasal insulin administration and the glucose level was appreciably reduced by 20 min. The lowest blood glucose concentration was found at 30 min with complete recovery of blood glucose by 60–90 min. All control subjects manifested symptoms and signs of a sympathoadrenal response to hypoglycemia at 30 min; however, spontaneous resolution occurred in all subjects without the need for exogenous glucose administration. Both the maximal extent of hypoglycemia and the time course of the hypoglycemic response were similar among different subjects (Figure 2).

Of these normal volunteers, 25 had serum insulin levels measured before and following intranasal insulin administration. All subjects demonstrated a prompt increase in the level of serum insulin (Figure 2), with peak concentrations occurring at the first time point monitored (10 min) and a return to baseline at 40–60 min. The range of peak insulin concentrations varied between 21 and 222 $\mu\text{U}/\text{ml}$ above baseline value with a mean of $103 \pm 49 \mu\text{U}/\text{ml}$. The decrease in blood glucose concentration was less variable ($54 \pm 14\%$ of normalized basal levels).

To further assess the reproducibility of serum insulin levels and blood glucose response to intranasal insulin, three subjects received the same dose (0.5 U/kg) of intranasal insulin in a 1% (w/v) deoxycholate aerosol on different days. Figure 3 shows that the fall in blood glucose in response to intranasal insulin on repeat testing was similar in each subject. Peak serum insulin levels were achieved by 10 min in all

cases, but were somewhat less reproducible than the glucose response.

We next determined whether insulin absorption across the nasal mucosa in the presence of 1% deoxycholate was dependent on the dose of insulin administered. Six normal subjects received graded doses of insulin by nasal spray. Figure 4 demonstrates that there was a linear dose response relationship between the mean increment in serum insulin levels and the dose of insulin administered. A dose of 0.1 U insulin/kg resulted in a small increase in serum insulin levels; 0.25 U/kg resulted in a mean increase of serum insulin level of 51 $\mu\text{U}/\text{ml}$, whereas 0.5 U/kg resulted in a mean increase of 103 $\mu\text{U}/\text{ml}$. The mean serum insulin level achieved at a dose of 0.5 U/kg was calculated from data on all subjects studied at this dose ($N = 25$). While each subject demonstrated a linear dose response relationship between the amount of insulin administered and the peak serum insulin level, there was considerable variation among subjects and this is reflected in the large standard deviations of the means for peak insulin level at each insulin dose.

We investigated both the time course of insulin appearance and the percentage of insulin absorbed across the nasal mucosa by comparing serum insulin levels following intranasal administration and following an intravenous bolus of insulin given to the same subject (Figure 5). Following the intranasal administration of 0.5 U/kg insulin in 1% deoxycholate, serum insulin levels increased above baseline by 2 min and reached a maximum at 10–12 min, returning to baseline by 50–60 min. In contrast, following intravenous administration of one-tenth of this dose (0.05 U of insulin/kg body weight), peak serum insulin levels were attained within

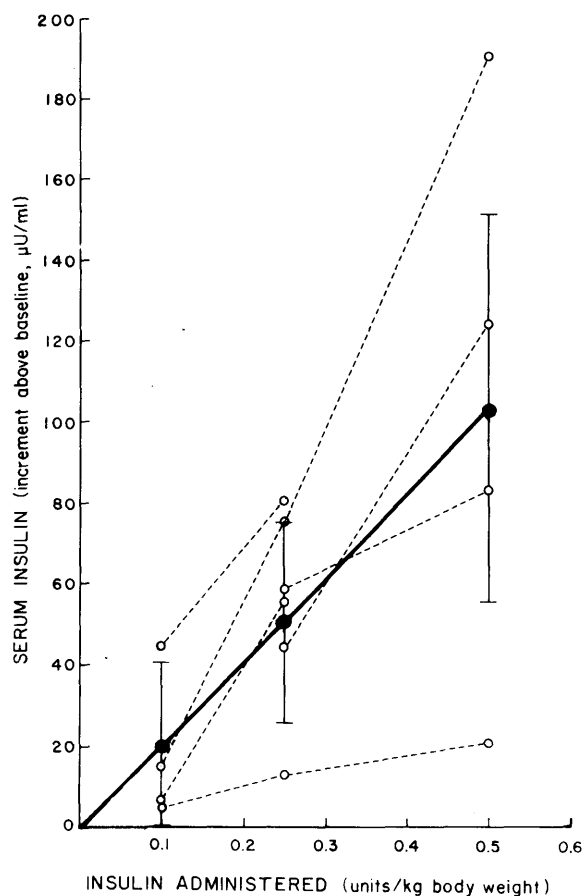


FIGURE 4. Insulin absorption following graded doses of insulin delivery. Six normal volunteers were administered graded doses of insulin (range 0.1–0.5 U/kg) in 1% (w/v) deoxycholate acid. Individual responses are shown by the open symbols and dashed line for each subject. The solid symbols and line represent the mean peak serum insulin concentration above baseline (for all subjects) achieved at each insulin dose. The numbers of subjects studied at each dose were: 0.1 U/kg, N = 4; 0.25 U/kg, N = 6; 0.5 U/kg, N = 25.

2 min and returned to baseline at about 30–40 min. Comparison of areas under the insulin curves allows us to estimate that insulin absorption was approximately 20% as efficient from the nasal spray as the intravenous injection. In three additional subjects, the kinetics of insulin absorption were indistinguishable from the results obtained in the subject shown in Figure 5. However, the percentage of insulin absorbed across the nasal mucosa varied. In the four subjects in whom comparison was made between insulin absorption after intranasal administration [with 1% (w/v) deoxycholate] and intravenous administration, the mean efficiency of transnasal absorption was 10%.

Figure 6 demonstrates the time course of intranasal insulin action in two type II diabetics. In both individuals, there was a prompt and sustained decrease in the level of blood glucose when compared with normal controls. The prolonged biologic effect in these subjects was not secondary to a sustained pattern of insulin absorption since the pattern of serum insulin levels were similar to the findings in control subjects.

The results for the four patients with type I diabetes mellitus are shown in Figure 7. After intranasal administration of in-

sulin, 0.5 U insulin/kg body weight, the blood glucose level decreased in each individual and serum concentrations of free insulin reached a peak by 10 min. Subject 9, with the greatest increment in serum free insulin concentration, had the greatest decrease in blood glucose level. Subject 13 was tested on two occasions. At first testing, serum free insulin increased only 8 μ U/ml, but blood glucose remained stable for 6 h. Following a second nasal insulin administration, serum insulin levels increased 32 μ U/ml over baseline and blood glucose declined from 240 mg/dl to 188 mg/dl. Thus, transnasal absorption of insulin was well below the mean of values for normal volunteers on both occasions in this patient. The half-time of disappearance of serum free insulin was minimally prolonged in patients with type I diabetes (normal controls = 6–8 min, type I diabetics = 8–20 min). Anti-insulin antibodies were detected in the sera of each individual, and these may have been responsible for the prolonged half-life of insulin. Like type II subjects, all four subjects with type I diabetes demonstrated a prolonged hypoglycemic response to intranasal insulin that persisted for as long as 4–6 h. This response, as in the type II subjects, was not due to sustained absorption or prolonged half-life of serum insulin.

Both normal volunteers and diabetics tolerated intranasal administration of insulin in 1% deoxycholate well, but reported mild nasal irritation lasting approximately 5–10 min and minimal nasal congestion lasting 5–15 min following administration. Deoxycholate alone reproduced this effect, and insulin administered in the absence of bile salts produced no nasal symptoms.

DISCUSSION

This study demonstrates that when insulin is administered in an aerosol with 1% deoxycholate, it traverses the nasal mucosa and rapidly passes into the circulation. The bile salt is necessary for this effect, since insulin alone (pH 7.4), when administered intranasally, neither increases serum insulin levels nor lowers blood glucose concentration. Furthermore, since the bile salt alone had no effect on the level of serum insulin or blood glucose, it is obvious that insulin and bile salt in combination are required for the observed metabolic effects.

Although investigators reported on the nasal administration of insulin as early as 1958, previous reports left many unanswered questions regarding the kinetics, the reproducibility, and the efficacy of this route of insulin administration.^{9–11} In all 25 normal subjects studied, the intranasal administration of insulin resulted in a prompt increase in serum insulin levels and a prompt and marked decrease in the blood glucose concentration. In the normals, restoration of euglycemia was attended by symptoms and signs of a sympathoadrenal response and presumably was caused by the combined release of epinephrine and glucagon, as expected for normal glucose counterregulation.¹⁵

In the control subjects, the reductions in the concentration of blood glucose after intranasal insulin administration were more uniform than were the increases in serum insulin levels. A number of factors may have contributed to these variations. First, as noted above, the volumes delivered by the spray applicator varied by approximately 10%. Second, the time at which serum insulin levels peaked varied from 5 to

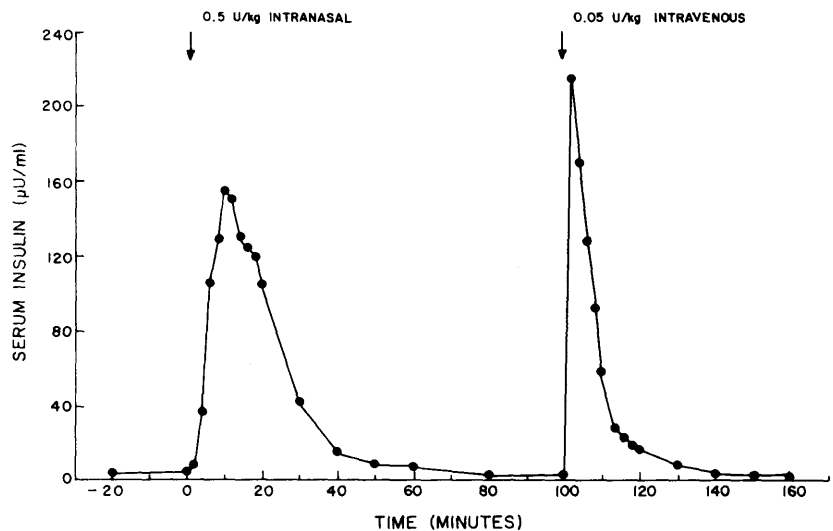


FIGURE 5. Serum insulin levels in an individual given 0.5 U insulin/kg as a nasal spray in 1% (w/v) deoxycholate followed by 0.05 U insulin/kg given as an intravenous bolus.

15 min after administration in different individuals, and this variability increased the data dispersion around the mean at each time point. Finally, there was more variability between different individuals than in the same individual when tested on two or three occasions. Control subjects ($N = 25$) could be divided into three subgroups. In seven, peak serum insulin levels after 0.5 U/kg insulin were greater than 130 $\mu\text{U}/\text{ml}$ above basal; in 13, peak serum insulin levels were 70–130 $\mu\text{U}/\text{ml}$ above basal; and in five, serum insulin levels were less than 70 $\mu\text{U}/\text{ml}$ above basal. Despite the intersubject variations, insulin absorption was dose-dependent in any single individual. The reasons for the intersubject differences are currently unknown.

The kinetics of insulin absorption across the nasal mucosa closely resembles that seen following intravenous rather than subcutaneous or intramuscular routes of administration. Thus, serum insulin levels peaked 10 min after nasal administration compared with 2 min after intravenous administration. Serum insulin levels are maximal 50–60 min after intramuscular injection and 120–180 min following subcutaneous injection.¹⁶ Direct comparisons of intranasal and intravenous insulin administration in the same subject demonstrated that approximately 10–20% of nasally administered insulin reaches the circulation. The fate of nasally administered insulin that does not enter the venous circulation is not known.

When compared with the response in normal volunteers, the pattern and time course of the hypoglycemic response to intranasal insulin in type I and type II diabetics were different. In type II diabetics, insulin was absorbed rapidly and its half-life was similar to that in controls. Peak serum insulin levels were higher than in controls and this is explained in part by the fact that these subjects were obese and insulin dosage was calculated on the basis of body weight. Hence, these obese subjects received proportionately more insulin per body surface area than did the normal weight volunteers. However, the most striking aspect of the response to intranasal insulin in type II diabetics was the prolonged hypoglycemic response, which lasted for as long as 5 h. Neither subject had ever been treated with insulin nor had detectable anti-insulin antibodies (Table 1). Moreover, both subjects had some degree of endogenous insulin resistance as evi-

denced by their elevated levels of serum insulin in the fasting state. It is interesting to note that neither subject had symptoms suggestive of a sympathoadrenal response during the prolonged period of relative hypoglycemia.

Compared with normal volunteers, the four type I diabetics demonstrated more variability both in regard to their serum insulin levels and their blood glucose responses following intranasal insulin. The mean peak increment in insulin levels after 0.5 U/kg insulin by nasal spray was lower in these type I diabetics than in our controls ($36.8 \pm 19 \mu\text{U}/\text{ml}$ versus $114 \pm 49 \mu\text{U}/\text{ml}$). The explanation for the lower serum insulin levels in these type I diabetics than in our normal controls

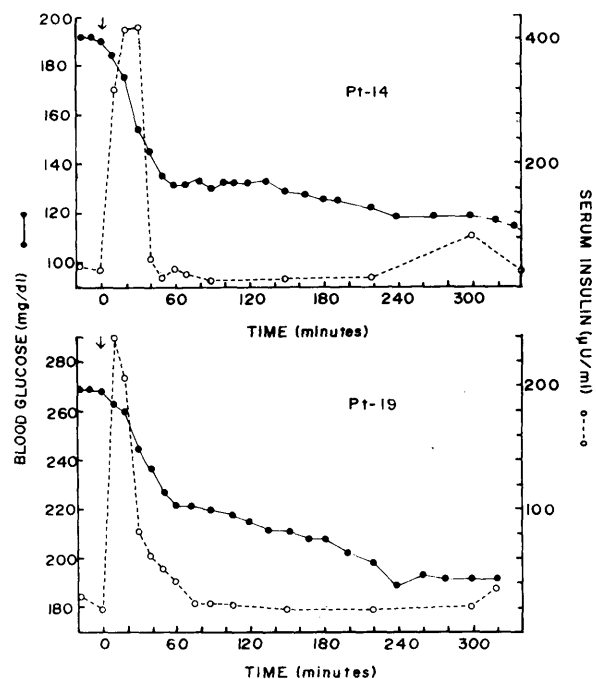


FIGURE 6. Serum insulin (○---○) and blood glucose (●—●) concentrations versus time for two subjects with type II diabetes mellitus. At time zero (arrows), 0.5 U insulin/kg was administered as a nasal aerosol with 1% (w/v) deoxycholate.

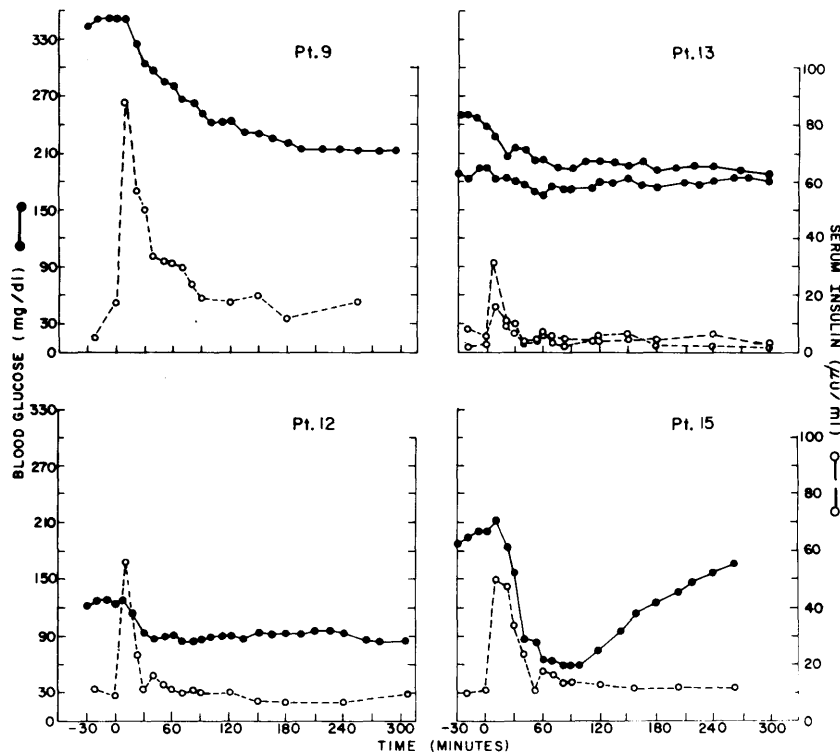


FIGURE 7. Serum insulin (○—○) and blood glucose (●—●) concentrations versus time for four patients with type I diabetes. The patients received 0.5 U insulin/kg body weight in 1% (w/v) deoxycholate as a nasal spray at time 0. One patient (subject 13) was studied on two occasions.

is not clear, but decreased transnasal insulin absorption or an artifact resulting from PEG precipitation of stored rather than fresh serum samples¹⁷ could be responsible. The half-life of serum insulin was also moderately prolonged in the patients, and this is probably explained by the presence of anti-insulin antibodies in their sera (Table 1). However, this prolonged half-life is probably not adequate to explain the prolonged effect of nasally administered insulin on blood glucose concentration in these subjects (Figure 7).

The blood glucose responses in the type I diabetics after intranasal insulin varied in magnitude as well as in duration compared with control subjects. Three of the four subjects demonstrated significant reductions in blood glucose concentration beginning 15–20 min following intranasal insulin. Two subjects maintained their lowest blood glucose concentrations (120 mg/dl below basal, subject 9, and 35 mg/dl below basal, subject 12) for the duration of the study (300 min). Subject 13 (Figure 7) had the smallest increment in serum free insulin concentration, and the smallest percent decrease in blood glucose concentration. It is possible that this subject was moderately insulin resistant, although neither her usual insulin dosage nor her insulin antibody titer (Table 1) supports this possibility. In the one type I diabetic with the shortest duration of insulin effect (subject 15), blood glucose began to rise after 2 h, coincident with the development of symptoms of a sympathoadrenal response.

The explanation for the prolonged duration of insulin effect in both type I and type II diabetics following intranasal insulin administration is not clear. Diabetic subjects often have impaired release of glucagon and epinephrine in response to insulin-induced hypoglycemia whether within the normal range¹⁸ or to frankly hypoglycemic levels.¹⁸ Such failure of glucose counterregulation in most of our diabetics could have contributed to the prolonged blood glucose effect that

we have observed. In fact, such a prolonged hypoglycemic effect in response to i.v. insulin has been attributed to a blunted glucagon response in a group of type I diabetics.¹⁵ Another possible explanation for the prolonged effect of insulin could be related to the observations of Gray et al.²⁰ who, using the euglycemic insulin clamp, found that in normal man the inhibition of glucose production by insulin extends for at least 50–60 min after discontinuation of intravenous insulin. Although data are not currently available in diabetics using this technique, it is possible that the duration of their response may be even more prolonged.

The current study suggests that the intranasal administration of insulin as a bile salt aerosol might have several advantages over currently available approaches to parenteral insulin administration. First, since no injection is required, intranasal insulin administration should have wide patient acceptability, especially among the very young, the very old, the blind, and the debilitated. Second, since insulin absorption is rapid (approaching that of i.v. insulin administration),¹⁶ this form of administration at mealtime could provide meal-related insulin levels more typical of those provided by normally functioning islet beta cells. After an intranasal insulin dose of 0.25 U/kg in normal volunteers, the mean peak insulin concentration was 51 μU/ml. This value approaches that seen postprandially in normal subjects,²¹ and is equivalent to 18 U of insulin in a 70-kg individual. We suspect that intensive regimens involving prandial administration of nasal insulin might be more widely accepted than intensive regimens involving conventional insulin injections or portable subcutaneous insulin infusion pumps.²²

The ultimate development of a clinically useful nasal spray for insulin treatment of diabetes is likely to depend on the local or systemic toxicity of the transport-enhancing agent. Deoxycholate, which was used in the present study, has

been shown to be toxic to the gastrointestinal mucosa when administered orally.²³⁻²⁵ Further, glycocholate, a conjugated bile salt that weakly enhances insulin absorption from the nose,¹⁰ causes ultrastructural abnormalities of the nasal mucosa.²⁶

Preliminary data from our laboratory demonstrate that all bile salts are not equipotent in their ability to promote insulin uptake across the nasal mucosa. Further, we have noted that local nasal irritation produced by a particular bile salt does not correlate with that bile salt's effectiveness as an adjuvant to insulin absorption. It is likely that a detailed investigation of the molecular properties of bile salts that determine their potency as promoters of mucosal transport will result in development of compounds with enhanced efficacy and minimal potential for local or systemic toxicity. Developments in this area should have wide applicability to other important pharmaceuticals that at present cannot be delivered to the systemic circulation by the enteral route.

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