PAPERS AND SHORT REPORTS

Insulin given intranasally induces hypoglycaemia in normal and diabetic subjects

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Abstract

Regular or crystalline insulin with sodium glycocholate as surfactant administered intranasally to normal volunteers induced hypoglycaemia and an increase in serum immunoreactive insulin concentrations. Serum C-peptide concentrations decreased or remained unchanged. Insulin administered intravenously to three of these subjects yielded a potency ratio of 1:8 for intranasal and intravenous insulin. In four insulin-dependent diabetics a cross-over study was performed on different days, insulin being administered once intranasally and once subcutaneously in a ratio of 1:9. In these patients the intranasal insulin was more effective than the subcutaneous insulin in preventing hyperglycaemia after breakfast. In four other insulin-dependent diabetics 11-hour monitoring was performed twice on two different days, insulin being administered in divided dosage sufficient to achieve a reasonable glycaemic profile. The average control was similar with the two routes of administration during the morning, whereas subcutaneous insulin was more effective than intranasal during the afternoon.

Introduction

Insulin is administered by injection, usually subcutaneously but occasionally intravenously or intramuscularly. Generally such routes of administration are satisfactory in terms of efficacy of treatment and compliance by patients. Severe reactions may, however, occur after subcutaneous injection, and many patients are reluctant to accept a regimen of regular daily injections.

Because of these problems, especially with subcutaneous administration of insulin, other routes have been sought. Giving insulin by mouth has been tried, but gastrointestinal proteolytic digestion remains a limiting factor.[1 2] The mucosa of the respiratory system, however, absorbs some inhaled materials—for example, vasopressin given for diabetes insipidus,[3] and luteinising hormone-releasing hormone,[4] which is used experimentally in reproductive endocrinology.

We report on the efficacy and safety of insulin administered by the nasal route in normal subjects and in insulin-dependent diabetic patients.

Subjects and methods

Six normal adults volunteered for a preliminary study. All were doctors or undergraduate medical students from this hospital, and were fully aware of the aims of the study as well as the possible hazards. After an overnight fast and no smoking they were studied in bed during the morning. Throughout the experiment they were connected to a Biostator (CGIIS, Miles-Ames, Ekhart, Indiana, USA), which allowed blood glucose concentrations to be checked every minute. After 15 minutes to ensure steady basal blood glucose concentrations, drops of solutions containing insulin (20 to 60 IU/subject) were inserted in to both nostrils and subjects asked to take a deep breath. In one subject insulin was administered twice, with a 90-minute interval. One or two experiments were performed on all subjects with two different insulin preparations on different days.

Control experiments were performed on the subjects to monitor basal blood glucose concentrations without insulin administration. In three subjects, insulin was also administered intravenously (0·1 IU/kg body weight): the activity of intranasal to intravenous insulin showed a ratio of about 1:8.

After establishing that a single dose of insulin given by the nasal route was effective and harmless in normal subjects we conducted a similar study on four diabetic inpatients who had been admitted for evaluation of metabolic state. All gave informed consent and underwent a cross-over study to compare the effect of a dose of insulin given subcutaneously with one nine times greater given intranasally. The patients' usual dose of subcutaneous insulin was used irrespective of whether this was the optimum morning dose. Five minutes after the

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subcutaneous or intranasal dose patients took their usual breakfast; blood glucose concentrations were checked by Biostator before insulin administration and for up to 60 minutes afterwards. We then monitored by Biostator four other diabetic inpatients for up to 11 hours. On two different days these patients received subcutaneous or intranasal insulin in divided doses sufficient to achieve reasonable metabolic control. During the days before the tests all diabetic patients had been treated with short-acting insulin only.

Solutions of commercially available regular insulin (Actrapid MC, Novo Industri, 40 IU/ml) or crystalline insulin (Hoechst, 1 mg = 27 IU dissolved with 0·01 M phosphate buffer pH 7·0, final concentration 110 IU/ml) were mixed with sodium glycocholate 1% w/v used as surfactant.[5] Serum immunoreactive insulin[6] and serum C-peptide concentrations[7] were determined by radioimmunoassay. Biostator determines blood glucose concentrations by an electrochemical sensor, enzyme-membrane system.[8]

Results

After intranasal administration of insulin a fall in blood glucose concentration occurred in all normal subjects (fig 1). This began at 12·3 ± 1·5 minutes (mean ± SEM; range 5-20 minutes) and continued for 51·5 ± 4·7 minutes (range 30-75 minutes). The fall was 41·9 ± 6·4% of basal blood glucose concentrations (range 9·3-76·5%) and averaged 1·9 ± 0·3 mmol/l (34·5 ± 5·3 mg/100 ml) (range 0·4-3·6 mmol/l; 7·0-65·0 mg/100 ml). Serum immunoreactive insulin concentrations increased in all subjects, peak values being observed 13·5 ± 0·7 minutes after insulin administration (range 10-15 minutes) and averaging 67·1 ± 16·6 mU/l (range 18-200 mU/l). When insulin was given twice, two episodes of hypoglycaemia and two distinct increases in serum immunoreactive insulin were observed. In all subjects there was good correlation between the amount of insulin administered and the peak immunoreactive insulin concentration reached and the area under the curve of immunoreactive insulin concentrations during the observation period ($r = 0{\cdot}66$; $p < 0{\cdot}05$).

Crystalline insulin produced slightly higher serum immunoreactive insulin concentrations than did regular insulin, but the difference was not statistically significant. In all subjects the larger the dose of insulin administered the more pronounced was the fall in the blood glucose concentration, though there was no clear relation between the amount of insulin given and the degree of hypoglycaemia induced.

In three normal subjects insulin was also administered intravenously: blood glucose concentrations in subject 1 were 1·3 mmol/l (23 mg/100 ml) after intranasal insulin and 0·3 mmol/l (5 mg/100 ml) after intravenous insulin; in subject 2 these values were 1·3 and 0·6 mmol/l (23 and 10 mg/100 ml) respectively; and in subject 3 3·2 and 1·0 mmol/l (58 and 18 mg/100 ml) respectively. These data suggested a potency ratio of about 1:8 for intranasal and intravenous insulin. Serum C-peptide concentrations remained steady in two and decreased in four of the six normal subjects.

In four insulin-dependent diabetic patients insulin was administered on two different mornings, once intranasally and once subcutaneously. The treatment was given five minutes before their usual breakfast, and the dosage ratio of intranasal to subcutaneous insulin was 9:1. During the one hour of observation blood glucose concentrations were lower after the intranasal dose than after the subcutaneous dose (fig 2).

Four other insulin-dependent diabetic patients were studied for up to 11 hours on two separate days. On one day insulin was given subcutaneously, and on the other day it was given intranasally. In both cases it was given in divided dosage to achieve an acceptable glycaemic profile. Two patients showed superimposable results throughout the two treatment periods (fig 3). One other patient disliked the repeated intranasal administration of insulin and withdrew after six hours of this treatment; in this patient and the remaining one, however, the glycaemic profiles were superimposable in the morning, whereas in the afternoon subcutaneous insulin was more effective. Total doses of insulin were 108 (nasal) compared with 42 (subcutaneous) IU in the first patient, and 324 compared with 65 IU, 378 compared with 50 IU, and 837 compared with 83 IU in the others.

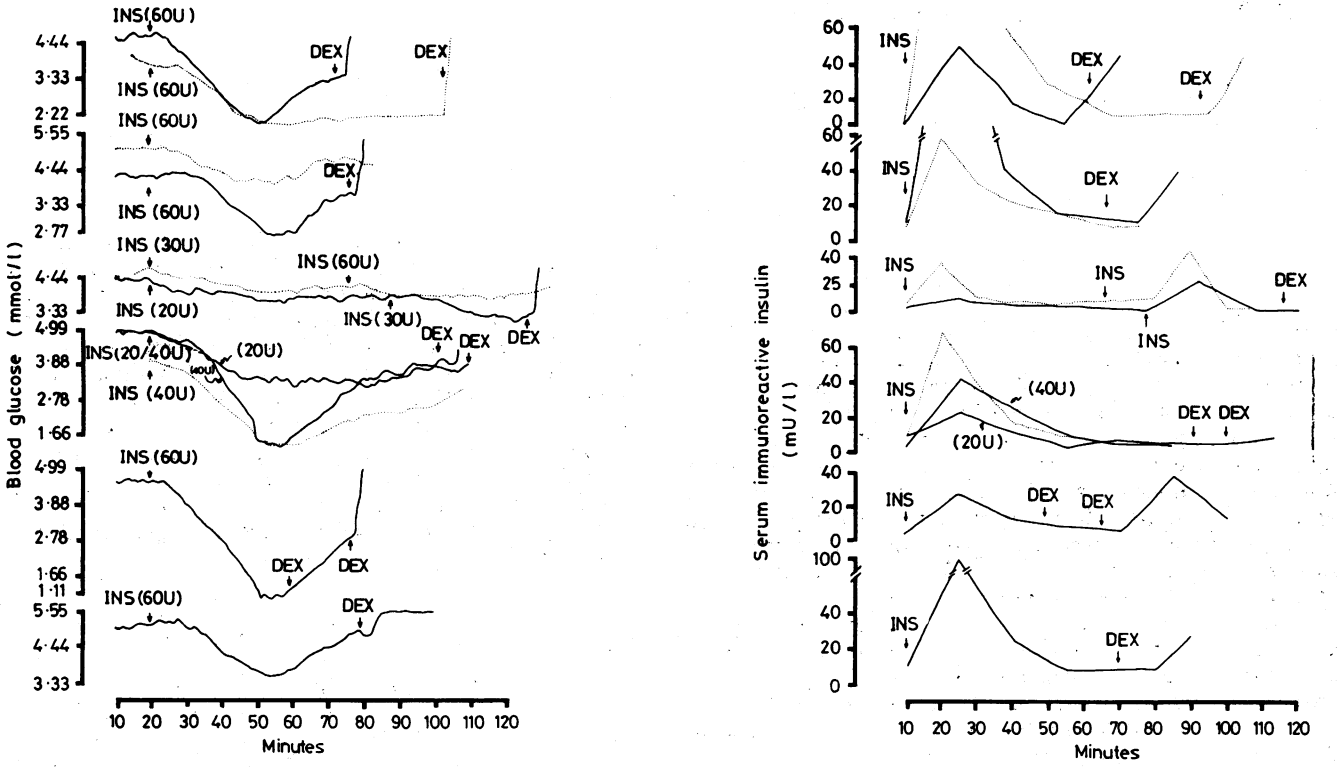

FIG 1—Blood glucose and serum insulin concentrations after intranasal administration of regular (——) or crystalline (- - - -) insulin at various dosages in six normal subjects. Arrows indicate timing of insulin (INS) and dextrose (DEX) administration. Doses of insulin used given in parentheses.

Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

Discussion

This study showed that in normal subjects insulin administered by the nasal route is well absorbed and induces hypo-

glycaemia. Serum immunoreactive insulin concentrations rose sharply after intranasal administration and showed a good correlation with the amount of insulin administered. Serum C-peptide concentrations were unaffected or decreased, indicating that pancreatic beta-cell function was inhibited and that hypoglycaemia was due to intranasally administered insulin. Hypoglycaemia began about 12 minutes after insulin administration, similar in this respect to hypoglycaemia induced by intravenous insulin. Compared with intravenous insulin, however, intranasally administered insulin induced a much more prolonged hypoglycaemia, which in two cases was stopped only with intravenous glucose. Though larger doses of insulin generally induced greater hypoglycaemia, only a weak correlation was found between the amount of insulin administered and the degree of hypoglycaemia obtained. Comparison of the hypoglycaemia induced by intravenous and intranasal insulin in three of the normal subjects suggested a nasal to intravenous potency ratio of about 1:8. No side effects were observed or reported by the subjects after intranasal administration of insulin. The only definite reactions were the usual phenomena which accompany hypoglycaemia.

Evidence of efficacy and safety of the nasal route in normal subjects prompted us to use the approach in insulin-dependent diabetics. When insulin was administered subcutaneously and by the nasal route to four such patients at doses in a ratio of 1:9, intranasal insulin was more effective than subcutaneous insulin in lowering fasting blood glucose concentrations and in counteracting rises in blood glucose concentrations after breakfast. In four other insulin-dependent diabetics intranasal and subcutaneous insulin were about equal in effectiveness during the morning, whereas intranasal insulin was slightly less effective during the afternoon. We cannot explain this difference, though in view of the small number of patients tested it might have been due merely to their day-to-day variation in glycaemic control. Alternatively, it might be that the doses used in our study were enough to induce hypoglycaemia and counteract rises of blood glucose concentrations induced by small amounts of food (breakfast) but not by larger amounts of food (lunch). A lessened response to insulin, on the other hand, is unlikely to have occurred during the limited (up to 11 hours) observation period, since in normal subjects repeated administration of insulin induced repeated episodes of hypoglycaemia.

Technical and theoretical problems are an obstacle to routine administration of insulin intranasally. Our experiments were performed with the aid of a monitor that allowed blood glucose concentrations to be checked every minute, which is quite different from the conditions in daily life. Also the way the insulin was prepared might be greatly improved. For instance, crystalline insulin was dissolved in a buffer and inserted into the nostrils as drops. Possibly other preparations, such as aerosolised insulin, would have better bioavailability if problems with the stability of insulin preparations and other technical difficulties could be solved. No side effects were observed after intranasal administration, though sensitisation is a theoretical risk. Commercially available insulin is a heterologous protein,

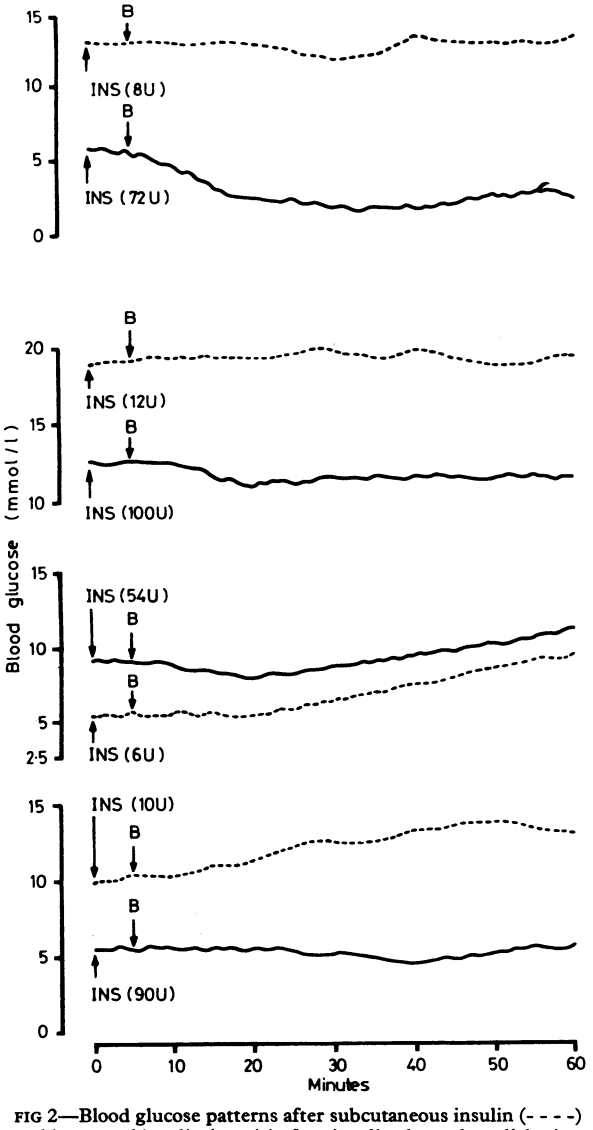

FIG 2—Blood glucose patterns after subcutaneous insulin (- - - -) and intranasal insulin (——) in four insulin-dependent diabetics. Doses of insulin were always in a 1:9 ratio. Arrows indicate timing of insulin (INS) administration and breakfast (B).

Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

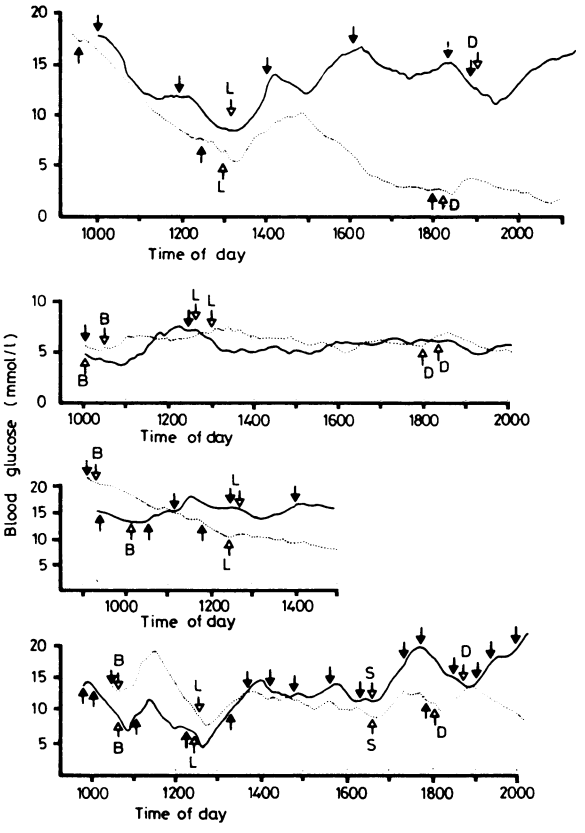

FIG 3—Daily variations in blood glucose concentrations after repeated administration of insulin subcutaneously (- - - -) and intranasally (——) in four insulin-dependent diabetics. Solid arrows indicate insulin administration. Open arrows indicate breakfast (B), lunch (L), snack (S), and dinner (D).

Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

and if mucosa became sensitised IgA antibodies might be formed and inactivate the insulin. Hence the recent availability of human insulin, produced by DNA-recombinant techniques,[9] appears to be more promising than porcine insulin.

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Failure of hyposensitisation in treatment of children with grass-pollen asthma

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Abstract

Twenty asthmatic children with laboratory proved bronchial reactivity to rye-grass pollen were studied over two consecutive grass-pollen seasons. In the first year 11 patients received preseasonal hyposensitisation treatment with an aqueous rye extract and nine received placebo injections. No treatment was given in the second year. Patients in both the active-treatment and placebo groups showed a pronounced clinical deterioration in their asthma during both pollen seasons. Serum concentrations of IgG-specific antibodies to the rye allergen before treatment were similar in both groups, but after immunotherapy and before the pollen season in the first year these antibody concentrations were raised significantly in the treated group ($p < 0.005$): by the middle of the pollen season the difference was no longer significant. IgE-specific antibodies showed a similar but non-significant pattern of response.

We found no evidence that limited hyposensitisation with a pollen extract is of any clinical benefit in seasonal asthma despite evidence of an immunological response.

Introduction

Hyposensitisation is effective in allergic rhinitis due to grass-pollen sensitivity,[1-3] and a favourable response to this treatment has been associated with increased production of so-called blocking antibodies and IgE antibodies specific for grass pollen.[1 2] The value of hyposensitisation in asthma is less clear, though there is some evidence of its value.[4 5] Studies which have failed to show a beneficial effect of hyposensitisation in asthma have been criticised on the grounds that bronchial reactivity to the allergen had not been demonstrated, the dose of allergen was inappropriate, or evidence of any immunological response to the treatment was lacking.

We have reported a deterioration in the asthma of children with grass-pollen bronchial reactivity during the grass-pollen season[6] and now report on the value of hyposensitisation to rye-grass pollen in such children. We evaluated the efficacy of treatment by assessing clinical symptoms, drug usage, and specific IgE and IgG antibody responses.

Subjects and methods

We studied 13 boys and seven girls aged 9 to 14 years (median 11 years). They were selected as follows. A questionnaire was distributed at random to 1000 children in the Melbourne metropolitan area. A total of 600 responses were received, from which 58 children with a history of wheeze consistent with asthma were selected. They were admitted to hospital and subjected to bronchial provocation tests with allergens. The 20 children included here gave immediate reactions to an aqueous rye-pollen extract, 11 of them had a further reaction at six to eight hours. All patients gave a positive reaction to a skin-prick test with rye grass, and 18 were also sensitive to *Dermatophagoides pteronyssinus* and other antigens.

All 20 children had had a history of recurrent wheeze for at least three years, and 11 had wheezed since early childhood. In the year before the study all had suffered at least four episodes of wheezing for at least 72 hours both during and outside the grass pollen season; 10 patients had had more than seven episodes. All patients were under the care of their family doctor and nine used prophylactic asthma medication throughout the study (eight inhaled sodium cromoglycate and one beclomethasone dipropionate). The one patient using beclomethasone and three of those inhaling cromoglycate also inhaled nebulised bronchodilator solutions regularly. All other patients had used oral or aerosol bronchodilators intermittently in the year before the study and continued to use these medications throughout.

The purpose of the study was fully explained to both the children and their parents and informed consent obtained.

Four months before the trial the children were admitted to the Royal Children's Hospital, Melbourne, for bronchial provocation tests with rye-grass pollen extract and blood sampling. They were then allocated at random to receive either active treatment ($n = 11$) or a placebo ($n = 9$). Those given active treatment underwent rush

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