

Sublingual Human Insulin for Hyperglycaemia in Type I Diabetes

Pages with reference to book, From 167 To 169

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Abstract

Objective: To investigate the hypoglycaemic effects of repeated sublingual doses of human insulin for the treatment of hyperglycaemia in type I diabetes.

Design: Clinical trial.

Setting: A Private clinic.

Method: Eight insulin dependent diabetic males with a mean age of 27 years (range 18-32 years) presenting with hyperglycaemia were given 1 U/Kg body weight of human soluble insulin in 5 equally divided doses at 15 min intervals, sublingually. Plasma glucose was estimated at 0,15,30,45,60,90, 120 and 150 min. Urine examination for glucose was done at 45 min intervals.

Results: The results showed that the mean plasma glucose before treatment was 19.93 ± 2.1 mmol/L. Hypoglycaemic effect was recorded at 15 min and reached a peak at 120 min when plasma glucose dropped to 10.9 ± 1.2 mmol/L ($p < 0.001$). No side effect was reported and insulin was tolerated well.

Conclusion: We concluded that sublingual human insulin in repeated doses has a hypoglycaemic effect and could be used to control hyperglycaemia in type I diabetes (JPMA 49: 167, 1999).

Introduction

Insulin is a polypeptide hormone that is used intramuscularly, intravenously or subcutaneously to treat insulin dependent diabetes. Many preclinical trials have been performed to study the possible insulin absorption from various non injection sites of administration including eye, rectum, nasal and buccal mucosa. Insulin was delivered with or without adjuvants. Rectal, nasal and buccal routes were 30% as effective as intramuscular route in experimental rats¹. Rats receiving eye drops or nose drops formulated with insulin plus saponins showed a dose-dependent hypoglycaemic response². Orally administered insulin even at high doses produced no hypoglycaemic effect³. The ability of human insulin to be absorbed from the oral cavity when it is instilled in the form of a simple solution or erythrocyte ghosts-insulin suspension has been demonstrated in streptozocin-induced diabetic rats⁴. Intranasal administration of insulin in normal individuals induced hypoglycaemia and increased plasma insulin levels^{5,6}. Review of literature showed that nasal route offers a promising alternative to parenteral administration for the treatment of diabetes⁷.

This study was conducted to investigate the possible hypoglycaemic effect of sublingual human soluble insulin on non ketotic hyperglycaemia in type I diabetes.

Patients and Methods

Eight diabetic male patients with age range of 18-32 years, (mean 27 years) presenting with hyperglycaemia were selected for the study after informed consent. They were on lente and soluble insulin treatment. All were subjected to a complete physical examination with estimation of blood pressure, pulse rate, temperature and state of hydration. Inclusion criteria were an elevated random plasma glucose and glycosuria with normal renal and liver function tests, complete blood picture, ECG

and chest X-ray.

Patients with ketoacidosis, vomiting, dehydration, convulsions, cardiovascular diseases, hepatic or renal impairment were excluded. Estimation of plasma glucose was performed at least 6 hours after the last dose of their subcutaneous insulin injection and last meal. Each patient had a fixed i.v. canula to receive hypertonic glucose in case of hypoglycaemia. Human soluble insulin 1 U/kg was given sublingually in 5 subsequent equally divided doses at 15 min intervals. The patients were asked not to swallow or spit their saliva. Plasma glucose was estimated at 0,15,30,45,60,90,120 and 150 min Urine examination for glucose was done at 45 min intervals. The patients were closely observed for any sings of hypoglycemia. Student t-test was used for statistical analysis.

Results

The random plasma glucose was elevated in all the eight patients with a mean value of 19.93 ± 2.1 nmol/L. Glycosuria was present in all the urine specimens ranging from +2 to +4. Following sublingual application of insulin, hypoglycaemic effect was recorded after 15 min and was observed to increase with subsequent doses of human soluble insulin (Table).

Table. Plasma glucose in 8 patients after sublingual insulin ($P < 0.001^*$)

Patients No.	Plasma glucose (mmol/L)							
	Time (min)							
	0	15	30	45	60	90	120	150
1	20	19	19	16.2	14.1	12.6	12	12.4
2	21.1	21	18.4	15.1	13	11.2	11.4	10.6
3	21.2	20.5	18.3	15.2	15.5	11	10.5	11.1
4	22.7	22.2	18.1	16.4	12.8	12.1	11.6	11.2
5	17.8	17.1	15.2	13.1	14.2	16.8	11.1	10.5
6	20.5	20.1	22.2	18.6	14.3	12.6	10.5	11.3
7	19.6	19.8	19	16.7	13.8	11.6	10.3	10.5
8	17	16.8	16.4	14.1	11.8	10.4	10.2	10.6
Mean $\pm$ SD	19.93 ± 2.1	19.5 ± 1.5	18.3 ± 1.8	$15.6 \pm 1.4^*$	$13.6 \pm 1.6^*$	$11.5 \pm 1.5^*$	$10.9 \pm 1.2^*$	$11.03 \pm 1.6^*$

The peak hypoglycaemic effect was seen at 120 min when the mean plasma glucose dropped to 10.9 ± 1.2 ($p < 0.001$). Glycosuria decreased after 2 hours. None of the patients developed emergency hypoglycaemia.

Discussion

The results of this clinical observation showed that absorption of human insulin through sublingual mucosa is possible resulting in reduction of plasma glucose. Mucosal route has been evaluated as a means of achieving systemic absorption for a number of polypeptides including calcitonin, growth hormone releasing factors, vasopressin analogues and insulin⁸. In one study nasal, buccal, sublingual and rectal absorption sites for insulin were isolated by ligation procedures or physical barriers and administration of insulin with absorption promoting adjuvant increasing insulin efficacy by each route³.

Absorption of insulin through buccal mucosa was demonstrated in another study using animal models resulting in hypoglycaemia which was enhanced in the presence of sorption enhancers⁹. A marked increase in the extent of hypoglycaemia was observed when insulin application time on buccal mucosa was from 0.5 to 1.0 h. The amount of insulin absorbed increased in the same order¹⁰. It has been suggested that a certain amount of time is required for insulin to be taken up by the buccal mucosa. In addition, intranasal insulin given at 0 min at a dose of 60 U or 120 U resulted in a 50% reduction in postprandial incremental glucose compared to placebo over the first 2 hours whereas treatment with 60 U both at 0 and 20 minutes lead to a 70% reduction over the 240 min postprandial level¹¹.

In our patients, insulin was given in repeated subsequent doses of 15 min intervals. This is made the mucosa exposed to insulin for a longer period and may allow a larger amount of insulin to be absorbed. In addition, insulin administered sublingually in repeated doses is in a liquid form and probably part of it may be in contact with buccal mucosa. So absorption occurs through two sites, mainly sublingual and partly via the buccal mucosa.

Using other sites of administration rather than subcutaneous or intravenous is a step forward to utilize non invasive or minimally invasive modes of administration. These sites including sublingual and buccal mucosa might help to reduce postprandial hyperglycaemia and improve plasma glucose levels. Further studies are required including addition of adjuvants to soluble insulin which may increase the rate of absorption. Estimation of serum insulin, C-peptide and other hormones should also be performed to authenticate the results.

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