CLINICAL RESEARCH

Hypotensive and sedative effects of insulin in autonomic failure

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Abstract

The haemodynamic responses to intravenous insulin (0.15 units/kg) were measured in five patients with chronic autonomic failure who were not receiving drug treatment. After the administration of insulin supine blood pressure fell steadily, with a substantial reduction even before the onset of hypoglycaemia. None of the patients showed the usual range of neuroglycopenic symptoms, but they all became drowsy, with increasing sedation as the blood glucose concentration fell. In four other patients with autonomic dysfunction intravenous injection of 25-50 ml of 50% glucose alone caused a striking, although transient, fall in blood pressure. Hypoglycaemia was reversed by a 10 minute intravenous infusion of 100 ml of 25% glucose; this did not lower blood pressure further and rapidly restored previous levels of alertness.

Consideration must be given to the hypotensive potential of insulin in patients with autonomic failure during an insulin stress test. The inability of these patients to show the usual manifestations of hypoglycaemia, plus the short lived, though pronounced, reduction in blood pressure after intravenous administration of 50% glucose, may further increase the risks of this procedure.

Introduction

Suspicion of endocrine and pituitary abnormalities in patients with autonomic failure may necessitate an insulin stress test. Insulin, however, may lower blood pressure substantially in some diabetic patients with an autonomic neuropathy¹ and to a lesser degree in tetraplegic patients after transection of the cervical spinal cord.² One of our patients with autonomic failure became severely hypotensive during an insulin stress test performed in the semi-recumbent position; his blood pressure did not rise after reversal of hypoglycaemia with intravenous, and later oral, glucose. We therefore investigated a group of patients with autonomic failure to see whether they were at risk from hypotension during an insulin stress test and during reversal of hypoglycaemia.

Patients and methods

We studied five patients (three men, two women), aged 48-65, with chronic autonomic failure of unknown aetiology. Two showed signs that the basal ganglia and cerebellum were affected as part of the syndrome of multiple system atrophy.³ All had severe postural hypotension, and sympathetic vasoconstrictor failure was confirmed by a series of physiological, pharmacological, and biochemical tests.⁴ The patients had impaired or absent chronotropic responses to atropine, indicating abnormal cardiac parasympathetic activity. The study was approved by the ethics committee, and each patient gave informed consent.

Studies were performed with the patient supine and horizontal. All drugs were withdrawn for 24 hours before the study, and observations were made in a temperature controlled laboratory (23°C). Non-invasive measurement of blood pressure and heart rate (with an automated sphygmomanometer; Sentron), forearm muscle blood flow (by mercury in Silastic strain gauge plethysmography), and skin temperature (with multiple thermistors over the forehead, cheek, neck, and index finger; Panlab) were made at frequent intervals. An indwelling cannula in a cubital vein was used for collecting blood for measurement of plasma glucose concentration (glucose oxidase method), plasma catecholamine concentration,⁵ and packed cell volume (Hawksley microhaematocrit) and for administering insulin. Hunger and sedation were assessed with a bipolar visual analogue scale.

After a 45 minute equilibration period baseline measurements were made for 30 minutes before intravenous administration of insulin (Actrapid) 0.15 units/kg. Blood samples were then taken every 15 minutes for laboratory measurement of plasma glucose concentration. Hypoglycaemia was reversed

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with intravenous infusion of 100 ml of 25% glucose over 10 minutes. Observations were continued for a further 60 minutes.

Four other patients (three men, one woman) with postural hypotension due to severe sympathetic failure, aged 42-68, were also studied after insertion of an intra-arterial catheter for assessment of their autonomic function. Of these four, two had chronic autonomic failure of unknown aetiology and two had primary amyloidosis. In these patients the cardiovascular responses to intravenous glucose (25-50 ml of a 50% solution) and a similar volume of isotonic saline were recorded. Observations after administration of intravenous glucose and saline were also made during intra-arterial studies in a subject undergoing testing who was found to have normal autonomic reflex activity. These studies were performed because hypotension had been recorded in tetraplegics with transection of the cervical spinal cord during the reversal of insulin hypoglycaemia with 50 ml of 50% glucose intravenously (C J Mathias, S M Wood, and H L Frankel, unpublished observations).

Results are expressed as means (SEM). Paired and unpaired *t* tests were used for statistical analysis.

Results

In the five patients with autonomic failure of unknown aetiology the mean blood pressure fell (by 8 (4) %) within five minutes after the administration of insulin and by 15 minutes had fallen by 21 (6) % (from 155 (6)/88 (5) to 121 (9)/70 (5) mm Hg; $p < 0.01$) (fig 1). At 15 minutes plasma glucose concentration was still above the accepted threshold of hypoglycaemia of 2.2 mmol/l. Hypoglycaemia occurred between 25 and 50 minutes (fig 2), and blood pressure fell further to a nadir of 116 (8)/60 (6) mm Hg (28 (4) %; $p < 0.01$). Glucose concentration rose to 8 (1) mmol/l after reversal of hypoglycaemia, but there was no further reduction in blood pressure.

The heart rate response to insulin varied: in two patients there was no change, while in the three others the heart rate rose during hypoglycaemia

FIG 1—Mean (SEM) systolic (●—●) and diastolic (○—○) blood pressure and heart rate in five patients with autonomic failure before and after intravenous insulin and after reversal of hypoglycaemia.

FIG 2—Mean (SEM) plasma glucose concentration and sedation score before and after intravenous insulin in five patients with autonomic failure and after reversal of hypoglycaemia. Dotted line indicates accepted threshold of hypoglycaemia of 2.2 mmol/l.

and fell after reversal. Forearm blood flow was unchanged for 20 minutes after the administration of insulin and rose with hypoglycaemia ($p < 0.01$ at 40 and 50 minutes) but only partially recovered after reversal (table). Skin temperature rose only in the index finger after hypoglycaemia and had fallen to basal values within 20 minutes after reversal. The packed cell volume remained unchanged until reversal of hypoglycaemia, when it fell transiently from 0.40 (0.02) to 0.37 (0.02) and 0.36 (0.02) after 60 and 75 minutes (each $p < 0.05$), respectively. Basal noradrenaline concentrations were 1.24 (0.47) nmol/l, being low (< 0.47 nmol/l) in two patients, in the intermediate range in one, and within the normal range in the remaining two. During hypoglycaemia the maximum rise was to 1.77 (0.59) nmol/l at 45 minutes (NS). Plasma adrenaline concentrations were 0.05 (0.05) nmol/l before and 1.58 (0.49) nmol/l after hypoglycaemia; this was substantially below the response expected in normal subjects (5.29 (0.55) nmol/l).²

In the four patients with autonomic dysfunction the intravenous injection of 25-50 ml of 50% glucose reduced blood pressure within 20 seconds of administration (from 122 (5)/56 (3) to 66 (5)/33 (4) mm Hg; $p < 0.001$) (fig 3).

FIG 3—Intra-arterial record showing blood pressure and heart rate in a patient with amyloidosis and severe autonomic failure before, during, and after 50% glucose intravenously. An equivalent amount of isotonic saline over a similar period caused no change in blood pressure.

Percentage changes in forearm blood flow, forearm vascular resistance, and skin temperature in index finger after administration of insulin. Hypoglycaemia usually occurred at 30-50 minutes and was reversed with intravenous glucose given between 50 and 60 minutes. Results are expressed as means (SEM)

	Time (min) after administration of insulin									
	0	10	20	30	40	50*	60	70	80	90
Forearm blood flow	0	-6.0 (5.0)	-3.4 (7.7)	+26.2 (24.1)	+91.0 (27.0)	+60.4 (30.8)	+35.0 (12.6)	+24.5 (15.2)	+28.9 (18.1)	+41.2 (33.2)
Forearm vascular resistance	0	-8.1 (7.0)	-22.2 (8.1)	-37.0 (9.8)	-54.1 (8.9)	-52.0 (7.1)	-37.8 (5.2)	-37.3 (6.4)	-35.8 (8.2)	-37.4 (12.8)
Skin temperature	0	-2.5 (1.1)	-4.0 (2.1)	-2.3 (0.9)	+4.1 (8.4)	+7.1 (9.2)	+7.1 (6.8)	+4.8 (5.2)	+1.1 (4.2)	+1.2 (3.5)

*Ten minute intravenous infusion of glucose begun 50 minutes after administration of insulin.

These observations were similar to those noted in tetraplegics during reversal of insulin induced hypoglycaemia. A similar volume of isotonic saline had no cardiovascular effects. Arterial concentrations of glucose measured in three patients 45-60 seconds after the administration of glucose were 20-25 mmol/l. In the subject with normal autonomic reflexes intravenous glucose did not lower blood pressure.

Discussion

In patients with autonomic failure intravenous insulin, in the standard dose used for pituitary testing, lowered blood pressure substantially even when they were in the supine position. Forearm muscle and cutaneous finger blood flow did not rise until the onset of hypoglycaemia, suggesting that peripheral vasodilatation did not contribute to the initial hypotensive response. The later dilatation in these vascular beds may have resulted from release of vasodilatory hormones induced by hypoglycaemia. Whether the early effects of insulin were due to a direct action on other vascular beds, such as the splanchnic circulation, is not known. Insulin influences vascular permeability and may have reduced effective plasma volume.⁶ We did not detect changes in the packed cell volume during hypoglycaemia, although our techniques may not have detected small changes sufficient to lower blood pressure in patients who lack corrective sympathetic cardiovascular reflexes. It is unlikely that there was a reduction in cardiac output as evidence from animals has indicated that insulin has positive inotropic effects.⁷ In normal subjects insulin does not lower blood pressure but increases plasma noradrenaline concentrations, presumably by stimulating sympathetic nervous activity.^{8,9} Insulin, however, lowers blood pressure in normal subjects after ganglionic blockade¹⁰ and causes a variable fall in pressure in patients with autonomic dysfunction due to diabetes mellitus or tetraplegia or after splanchnic denervation.^{12,11} In our patients impaired sympathetic vasoconstriction, in the face of unexplained vasodilatation especially in central vascular beds, probably accounted for the fall in blood pressure.

After hypoglycaemia the heart rate rose in three patients, but modestly, considering the fall in blood pressure. This reflected the degree of cardiac vagal impairment in our patients and also their inability adequately to influence sympathoadrenal activity during hypoglycaemia.¹² This probably also accounted for their lack of symptoms, such as sweating, during neuroglycopenia. Sedation was the only consistent sign of hypoglycaemia and was readily reversed by parenteral glucose. Similar observations were made, though no measurements taken, in patients with autonomic dysfunction due to tetraplegia, who are also unable to raise their plasma adrenaline concentrations during insulin induced hypoglycaemia.²

It is standard practice to reverse hypoglycaemia with either oral glucose or 50 ml of 50% glucose intravenously, or both. Oral glucose in these patients can cause a considerable (up to 32%) and prolonged (up to two hours) reduction in supine blood pressure.¹³ Observa-

tions in the four patients with autonomic dysfunction indicated transient but pronounced hypotension during the administration of intravenous glucose. This did not occur with isotonic saline, thus favouring a direct vascular effect of hyperosmolar glucose. As a compromise we therefore used the slow administration of 25% glucose, which did not lower blood pressure further.

Our studies indicate that in patients with autonomic failure who have impaired sympathoadrenal activity insulin causes a substantial fall in supine blood pressure. This can be expected to cause an even greater postural fall in blood pressure in these patients. Oral glucose and rapid injection of 50% glucose intravenously may lower blood pressure further and should be avoided. The hypotensive effects of insulin, the lack of usual neuroglycopenic symptoms, and the potential of glucose to lower blood pressure further should be borne in mind in these patients when they undergo insulin stress tests. Whether similar responses would occur in other groups with autonomic dysfunction, such as the elderly and those taking drugs that impair autonomic function, is not known. We suggest, however, that in these patients adequate precautions are also taken.

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