Intermediate acting insulin given at bedtime: effect on blood glucose concentrations before and after breakfast

A J FRANCIS, P D HOME, I HANNING, K G M M ALBERTI, W M G TUNBRIDGE

Abstract

Six C-peptide deficient diabetics receiving twice daily mixtures of short and intermediate acting insulins were selected for study because of persistently raised blood glucose concentrations before and after breakfast. They were investigated to assess the effect of moving their evening injection of intermediate acting insulin to bedtime. The patients’ usual twice daily insulin treatment was optimised and compared with the bedtime regimen during inpatient metabolic studies and an outpatient crossover study. With the conventional injection regimen blood glucose concentration rose sharply from 0500 to reach a fasting mean value of 10 ± SE 1.6 mmol/l (180 ± 29 mg/100 ml) and 16.8 ± 2.2 mmol/l (303 ± 40 mg/100 ml) after breakfast. By contrast, when the evening dose of intermediate acting insulin was delayed until bedtime the nocturnal rise in blood glucose concentration started later and was significantly lower both fasting (7.5 ± 1.1 mmol/l (135 ± 20 mg/100 ml); p<0.02) and after breakfast (13.2 ± 1.4 mmol/l (238 ± 25 mg/100 ml); p<0.02). Fasting blood concentrations of ketone bodies (3-hydroxybutyrate) were also significantly decreased. Plasma free insulin concentrations showed the predicted changes in five of the six patients. Blood glucose profiles collected over four months during the outpatient study confirmed the beneficial effect of giving intermediate acting insulin at bedtime.

Introduction

Many patients treated with twice daily insulin injections encounter difficulty in controlling fasting blood glucose concentrations and concentrations after breakfast. Although satisfactory control is often regained during the remainder of the day and for the first part of the night, the blood glucose concentration is again raised next morning. The aetiology of this morning rise in blood glucose concentration is not well understood, but a close inverse correlation exists between fasting blood glucose and free insulin concentrations. Thus fasting hyperglycaemia may be a consequence of the relative deficiency in free insulin available from an injection some 14 hours earlier. As the morning rise in blood glucose concentration often starts before the patient wakes it cannot be averted by the morning insulin injection. The evening insulin dose is limited by the risk of nocturnal hypoglycaemia. We therefore studied the effect of delaying the evening dose of intermediate acting insulin until bedtime to assess whether it improved nighttime control or influenced the early morning rise in blood glucose concentrations.

Patients and methods

Six insulin dependent diabetics were selected for study because of a persistent increase in fasting blood glucose concentrations (>10 mmol/l (180 mg/100 ml)) or concentrations after breakfast (>15 mmol/l (270 mg/100 ml)). The table gives the clinical details of the patients. None had any other metabolically important illness or was taking any medication other than insulin. They had all been using a twice daily mixture of short and intermediate acting highly purified porcine insulins for at least two years.

During a three month observation period the patients monitored their blood glucose concentrations at home using BM 20-800 Glycemie strips (Boehringer). In addition, before each clinic visit a series of seven blood samples was collected (before and after breakfast, lunch, and dinner, and at bedtime) for laboratory analysis of glucose concentrations using Sarstedt capillary tubes. Insulin and diet were adjusted as necessary. Particular attention was paid to adjustment of the evening dose of intermediate acting insulin to decrease fasting blood glucose concentrations while avoiding nocturnal hypoglycaemia.

After optimisation of blood glucose control the patients were admitted for two overnight metabolic profiles (from 1630 until 1200 the next day); in random order they received their usual dose of inter-

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mediate acting insulin either at 1730 ("conventional") or at 2200 ("bedtime"). The short acting insulin was given at 1730 on both occasions. Morning insulin and diet were unchanged. Similar activity was encouraged on both days of study. All insulin injections were given into the subcutaneous tissue of the lateral thigh.

On admission a polyethylene cannula was inserted into a forearm vein and its patency maintained by flushing with saline 0·15 mol (9 g.)1 after each blood sample. Blood samples were taken hourly from 1700 until 1200 the next day. Blood glucose concentration was measured immediately using a glucose oxidase electrode (Yellow Springs Instruments). Blood for estimation of lactate, pyruvate, glycerol, alanine, and 3-hydroxybutyrate was immediately deproteinised in 0·5 mol (50 g.) perchloric acid/1 and assayed by standard fluorimetric techniques.8 Plasma for measurement of free insulin concentrations was separated immediately by centrifugation and later extracted with polyethylene glycol7 before radioimmunoassay.9 Serum cortisol and growth hormone concentrations were measured by immunoassay and glucagon by extraction radioimmunoassay.10 Plasma catecholamine concentrations, assayed by high performance liquid chromatography,11 were estimated before breakfast and during nocturnal nadir in blood glucose concentration.

After the inpatient studies patients were randomised between the two injection regimens for an outpatient crossover trial. Each arm of the study lasted four months, the patients being assessed monthly. Before each clinic visit a series of seven blood samples was again collected for laboratory analysis, samples being taken before and one and a half hours after the three main meals and at bedtime. All episodes of symptomatic hypoglycaemia were recorded. In addition, overnight urine was collected monthly for estimation of glucose excretion and the ratio of cortisol to creatinine concentrations.12 Glycosylated haemoglobin concentration was measured at entry to the trial, at the crossover, and at the end of the study.13 Statistical analysis was by Student's paired t test. Results are presented as mean ± SE unless otherwise stated.

Results

INPATIENT STUDY

When both short acting and intermediate acting insulin were given together the evening meal a nadir in blood glucose concentrations occurred between 0200 and 0300 (3·5 ± 0·4 mmol/1 (63 ± 7 mg/100 ml)); the concentrations then rose steeply from 0500 to reach 10·0 ± 1·6 mmol/1 (180 ± 29 mg/100 ml) before breakfast and a peak after breakfast of 16·8 ± 2·2 mmol/1 (303 ± 40 mg/100 ml) (fig 1). When the intermediate insulin was delayed until 2200 the nadir in blood glucose concentration occurred later, at 0400, but was of a similar value (3·4 ± 0·5 mmol/1 (61 ± 9 mg/100 ml)); the morning rise in blood glucose concentration also started later, at 0600 (fig 1), reaching a fasting value of 7·5 ± 1·1 mmol/1 (135 ± 20 mg/100 ml) and 13·2 ± 1·4 mmol/1 (238 ± 25 mg/100 ml) after breakfast. These blood glucose concentrations were significantly lower (p < 0·05) from 0500 to 1000. Symptomatic hypoglycaemia did not occur with either regimen. In one patient blood glucose concentration fell below 2·5 mmol/1 (45 mg/100 ml) during the night. This occurred with both regimens but was more prolonged when insulin was given at the conventional time.

After bedtime administration of the intermediate acting insulin plasma concentrations of free immunoreactive insulin were lower during the late evening but remained higher overnight in five of the six patients (fig 2). A strong negative correlation (r = −0·74, p < 0·05) was seen between fasting plasma free insulin and blood glucose concentrations (fig 3). The lower blood glucose concentrations after

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<th>Insulin dose in</th>
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*All patients had undetectable concentrations of C-peptide one and a half hours after breakfast and normal plasma creatinine concentrations.

Fig 1—Mean (±SE) blood glucose concentrations during conventional twice daily insulin treatment (●—●) and with intermediate acting insulin given at bedtime (○—○). Stripped area indicates normal range. *p < 0·05.

Conversion: SI to traditional units—Glucose: 1 mmol/l = 18 mg/100 ml.

Fig 2—Profiles of plasma free insulin concentrations in six diabetics during conventional twice daily injection treatment (●—●) and with intermediate acting insulin given at bedtime (○—○). In all patients C-peptide was undetectable.
bedtime administration of insulin were thus associated with higher plasma concentrations of free insulin.

Concentrations of 3-hydroxybutyrate rose to abnormal values with both regimens towards the end of the overnight fast (fig 4). After bedtime injection of intermediate acting insulin this rise started later and concentrations before breakfast were significantly lower (0.43 ± 0.10 mmol/l v 0.75 ± 0.16 mmol/l; p < 0.05). No significant differences in lactate, pyruvate, glycerol, or alanine concentrations were seen between the two insulin regimens.

Cortisol profiles followed the normal diurnal rhythm. Only the one patient who became hypoglycaemic showed a counterregulatory rise in cortisol concentration, but this was small compared with the normal diurnal rise at dawn. No counterregulatory response in concentrations of glucagon, growth hormone, or catecholamines was seen. With both regimens, however, there was a rise in plasma glucagon concentration from 0500 (61 ± 5 ng/l) to 0900 (101 ± 14 ng/l) accompanying the initial rise in blood glucose concentration (fig 5).

**OUTPATIENT STUDY**

Blood glucose concentrations both before and after breakfast were lower with bedtime administration of intermediate acting insulin (11.1 ± 1.0 v 7.4 ± 0.9 mmol/l) (200 ± 18 v 133 ± 16 mg/100 ml) before; 11.3 ± 0.9 v 7.7 ± 0.9 mmol/l (204 ± 16 v 139 ± 16 mg/100 ml) after; p < 0.05) (fig 6). Values for the rest of the day were not significantly different. Overnight urinary glucose excretion was similar with both insulin regimens (32 ± 12 mmol (5.8 ± 2.2 g) with the conventional regimen v 25 ± 10 mmol (4.5 ± 1.8 g) with insulin given at bedtime). There was no increase in the ratio of cortisol to creatinine in the urine collected overnight. Concentrations of glycosylated haemoglobin did not change during the study, being 11.0 ± 0.8% at entry, 10.6 ± 0.8%, with the conventional regimen, and 10.4 ± 0.4% at the end of the bedtime regimen.

**Discussion**

Appreciably increased blood glucose concentrations before and after breakfast are a common problem in insulin treated diabetics. The concentrations are highest at these times in over 45% of patients performing laboratory measured home blood glucose profiles, and in half of these the concentrations before and after breakfast exceed equivalent observations later in the day by over 5 mmol/l (90 mg/100 ml) (A J Francis et al, unpublished observations). As noted by others and confirmed in the present study, blood glucose control in these patients is often reasonably acceptable for the rest of the day.

Delaying the evening injection of intermediate acting insulin by four and a half hours delayed the nadir in blood glucose concentrations during the night and reduced the fasting
and the peak concentrations after breakfast in both the inpatient and outpatient parts of our study. The inpatient study showed a reduction in blood glucose concentration of 2-4 mmol/l (36-72 mg/100 ml) from 0600 until 1100. Profiles of ketone body concentrations were also much closer to normal with bedtime administration of insulin. Concentrations of glycosylated haemoglobin did not improve, which reflects the relatively insensitive nature of this assay and the influence of variations in blood glucose control during the rest of the day, including perhaps relatively higher blood glucose concentrations in the late evening and early part of the night.

The results confirm previous observations that the morning rise in blood glucose concentration is not the result of hyper-glycaemia1 4 and begins in the depths of the night.1 2 The inverse relation between fasting blood glucose and plasma free insulin concentrations (fig 3) is also confirmed.4 5 The differences in free insulin concentrations, however, cannot be the sole determinant of metabolic control, for when the intermediate acting injection was delayed by four and a half hours the nocturnal nadir and subsequent morning rise in blood glucose concentration occurred only one to two hours later than normal (fig 1). Closed loop studies, when insulin delivery is determined by plasma glucose concentrations, have suggested that there might be a requirement for increased insulin delivery towards the end of the night,15 16 though during open loop studies (continuous subcutaneous insulin infusion) no rise in blood glucose or ketone body concentrations was found.17 18

Counterregulatory hormones are the prime candidates for secondary contributors to these phenomena. Our patients had a normal diurnal rise in cortisol concentrations and a coincident abnormal rise in plasma glucagon concentrations (fig 5). Cortisol at these concentrations does not influence metabolic control when insulin concentrations are adequate19 but does aggravate hyperglycaemia and ketosis in patients deprived of insulin20 or maintained on a fixed basal insulin infusion.21 Cortisol might therefore have been interacting with falling insulin concentrations in our patients. The lack of suppression of secretion of glucagon by hyperglycaemia is also consistent with insulin deficiency,22 and glucagon too requires hypoinsulinaemia before it affects glucose homeostasis or lipolysis.23

This report confirms results of previous uncontrolled studies of bedtime syringe24 or jet25 injection of insulin in which improvements in blood glucose concentration were just as likely to have been due to increased attention and education. Longer acting insulin preparations (ultralente) have been unsuccessful in controlling hyperglycaemia before and after breakfast whether given in the morning2 7 or evening.1 Continuous subcutaneous infusion of insulin gives stable overnight insulin concentrations,13 which may explain its success in improving fasting hyperglycaemia.26 28 29 For most patients, however, treatment is by injection. The regimen described here is easy to initiate in outpatients, and dosages do not have to be changed. Unlike a third, midday injection,1 an injection at bedtime is well tolerated. At this expense it provides greatly improved morning metabolic control.

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