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Timing of pre-breakfast insulin injection and postprandial metabolic control in diabetic children

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Summary and conclusions

A peak period of hyperglycaemia in insulin-dependent diabetics occurs after breakfast. A randomised crossover study was performed on nine diabetic children at home to study the effect of varying the time of their morning mixed injection of Monotard and Actrapid insulin on this hyperglycaemic peak. Performing the study at home minimised the children's stress.

After diabetic control had been improved children injected their insulin 30 minutes (early injection) or five minutes (late injection) before breakfast on two consecutive Saturday mornings. Blood samples were taken at 30-minute intervals over 3½ hours and analysed for concentrations of glucose, insulin, C-peptide, pyruvate, lactate, alanine, and ketones. Diet, insulin dose, and exercise were kept the same on both test days.

The mean blood glucose concentration at breakfast (0 minutes) was 11 mmol/l after the early injection and 10 mmol/l after the late injection. Subsequent concentrations were consistently lower with the early injection regimen than the late regimen. The greatest difference between values in the two groups was 3.7 mmol/l at 150 minutes. Mean plasma insulin concentrations were lower in the children on the early regimen than in those on the late regimen at 30 minutes before breakfast but higher at 0 minutes and thereafter. There were no significant differences in mean concentration of inter-

mediary metabolites between the two injection regimens. These were mainly within the normal range for healthy young adults except for the ketone concentrations, which were raised with both injection regimens until 180 minutes after breakfast.

These results suggest that the timing of the morning injection of insulin is important in the control of postprandial hyperglycaemia in diabetic children.

Introduction

It is established that the management of diabetes mellitus should include a serious attempt to keep blood glucose concentrations as close to normal as possible.¹ The diurnal variation in blood glucose concentration with various insulin regimens has been well documented in diabetic adults^{2,3} and children (G Werther, MSc thesis, Oxford University, 1978) by using 24-hour sampling methods in hospital. Despite differences in regimen, a hyperglycaemic peak usually occurs after breakfast.^{2,3} Factors that may contribute to this hyperglycaemia include insulin deficiency, relatively high carbohydrate breakfasts, and rebound from nocturnal hypoglycaemia.

Insulin deficiency should be improved by increasing the interval between the morning insulin injection and breakfast. A preliminary survey of 30 diabetic children attending our clinic showed that for most of them this interval was 15 minutes or less, either for convenience or for fear of hypoglycaemia. We performed this study to see whether the minimal disruption of giving the morning insulin injection 30 minutes rather than five minutes before breakfast could significantly reduce postprandial hyperglycaemia without producing preprandial hypoglycaemia in diabetic children. Our study also aimed at evaluating the acceptability of metabolic studies on such children at home.

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Methods

CLINICAL METHODS

We examined nine children from the Oxford paediatric diabetic clinic. They came from stable, co-operative families and were approached with the approval of their general practitioners and the Oxford ethical committee. Parents and children gave their informed consent.

The children's mean age was 13.8 years (range 10.3-16.7) and their mean duration of diabetes 4.3 years (range 1.1-13.2). They were managed on a carbohydrate-regulated diet and a once-daily insulin injection of Monotard and Actrapid (Novo) given together before breakfast. Their mean total insulin dose was 49 units/day (range 28-86) and the mean insulin dose per kg body weight was 0.95 U/kg (range 0.51-1.39).

The children's mean height centile was the 59th (range 25th-97th), and their mean weight centile was the 80th (range 50th-97th). Outpatient control over the past year had been good in five children with most urine tests before three main meals each day yielding negative results with the two-drop Clinitest method⁴ without hypoglycaemic symptoms. Control had been average in the remaining four children with most urine tests before three main meals each day showing under 1% glycosuria by this Clinitest method. Each child was studied on two consecutive Saturday mornings. On one morning the insulin injection was given 30 minutes before starting breakfast (the early group) and on the other five minutes before starting breakfast (the late group). Test order was randomised for each child by tossing a coin.

In the two to four weeks before the test days diabetic control was assessed and improved by using 24-hour home urine collections for estimating glucose excretion and measuring blood glucose concentra-

tions. Capillary blood was obtained by fingerprick using the Autolet method (Owen Mumford) and blood glucose concentrations estimated using the Eytone-Dextrostix system (Ames) at up to seven sampling times over the day on one to three days. Appropriate changes in treatment were made to achieve preprandial blood glucose concentrations of 7.5 mmol/l or less. Insulin dose and amount of carbohydrate prescribed were then kept the same for the two test days. On test Saturdays and the preceding Friday evenings exercise and diet were standardised for each child in consultation with the clinic dietitian.

On test mornings one of us (ALK) arrived at the child's home at 7 am. An 18-gauge Teflon intravenous cannula (Abbott Laboratories) was inserted into an antecubital vein under local anaesthesia (1% lignocaine) and connected to a three-way tap. The tap was kept patent by flushing with saline after taking each sample. Samples were taken at 30-minute intervals for 3½ hours, and the cannula was then removed. Breakfast was eaten at 8.00-8.15 am and a snack at 10.15-10.20 am. The children rested for 10 minutes before each sample was taken. Between sampling times they watched television, read, or talked, sitting in the living room of their homes.

LABORATORY METHODS

At each sampling time 4-ml blood samples were divided between ice-cold lithium heparin and 5% w/v perchloric acid and kept at 4°C. The acidified samples were neutralised within 48 hours and assayed for glucose, ketones, pyruvate, and alanine concentrations by using enzymatic methods.⁵ The heparinised samples were separated within four hours and the plasma stored at -20°C until required for radioimmunoassay for free insulin⁶ (antibody supplied by P Sönksen) after polyethylene glycol extraction⁸ and for determinations of C-peptide concentration⁷ (antibody supplied by Novo).

STATISTICAL METHODS

Differences between pairs of means were tested for significance by Wilcoxon's rank sum test. In presenting the absolute values for glucose and insulin concentrations a mean value was used in five places where an individual value was missing. The insulin values are based on the results in eight children because of incomplete antibody extraction in one.

Results

Figure 1 shows the mean blood glucose concentrations ($\pm$ SEM) in nine children at both times of injection. Means of all the concentrations before breakfast were: in the early group 10.7 mmol/l (range 3-20) and in the late group 10.2 mmol/l (range 4-17). Four children had fasting blood glucose concentrations below 10 mmol/l before the early injection. The mean fasting concentration in these children was 5.7 mmol/l at the time of injection (-30 minutes) and 5.9 mmol/l at breakfast (0 minutes). All postprandial blood glucose concentrations were lower after the early injection than after the late injection. Table I shows the mean values for both injection regimens.

TABLE I—Mean postprandial blood glucose concentrations mmol/l in nine diabetic children on early or late insulin injection regimens

	Time after breakfast (min)			
	90	120	150	180
Early injection regimen	16.8	14.4*	12.9	12.6
Late injection regimen	19.4	17.6*	16.6	14.8

*Difference between means significant ($p < 0.05$).

Figure 2 shows the mean changes in blood glucose concentration from that at 0 minutes. Differences between the two groups in mean blood glucose concentrations were: at 60 minutes 2.45 mmol/l ($p < 0.005$), at 90 minutes 3.14 mmol/l ($p < 0.005$), at 120 minutes 2.71 mmol/l ($p < 0.005$), at 150 minutes 2.67 mmol/l ($p < 0.005$), and at 180 minutes 3.72 mmol/l ($p < 0.005$).

Figure 3 shows the mean plasma insulin concentrations ($\pm$ SEM) in eight children on both injection regimens. Mean basal values (at

FIG 1—Blood glucose concentrations in nine diabetic children giving morning insulin injection. Bars show SEM. $\uparrow$ = Time of injection. $\circ$ --- $\circ$ = Insulin given 30 minutes before breakfast (early injection). $\bullet$ — $\bullet$ = Insulin given five minutes before breakfast (late injection). * = Difference between mean values significant ($p < 0.05$).

FIG 2—Changes in blood glucose concentrations from value at breakfast time in nine diabetic children giving morning insulin injection. * = Difference between corresponding mean values significant ($p < 0.005$). For rest of key to figure see legend to fig 1.

FIG 3—Plasma insulin concentrations in nine diabetic children giving morning insulin injection. * = Difference between corresponding mean values significant ($p < 0.05$). For rest of key to figure see legend to fig 1.

— 30 minutes) were: in the early group 7.5 mU/l and in the late group 8.1 mU/l. All subsequent values were higher after the early injection than the late.

Eight of the nine children had detectable C-peptide concentrations. The remaining child had had diabetes for 13 years (twice as long as the others). Figure 4 shows the mean C-peptide concentrations ($\pm$ SEM) in the eight children on both injection regimens. The range of C-peptide concentrations was large: fasting values ranged from 0.0146 pmol/ml and peak values from 0.021–0.78 pmol/ml. The mean concentration at breakfast was 0.066 pmol/ml and mean peak concentration 0.169 pmol/ml, which coincided with the mean peak blood glucose concentration at 90 minutes. There was no significant difference in C-peptide concentrations between the two injection regimens.

FIG 4—Plasma C-peptide concentrations in nine diabetic children giving morning insulin injection. For key to figure see legend to fig 1.

The values obtained for the intermediary metabolites blood lactate, pyruvate, and alanine lay mainly in the normal ranges for healthy young adults,³ and there were no significant differences between the two injection regimens. Blood ketone concentrations were abnormally

TABLE II—Mean ($\pm$ SEM) blood ketone concentrations mol/l in nine diabetic children on early or late insulin injection regimens

	Time from breakfast (min)		
	– 30	30	180
	0.25 $\pm$ 0.1	0.28 $\pm$ 0.1	0.09 $\pm$ 0.015
	0.4 $\pm$ 0.1	0.44 $\pm$ 0.1	0.09 $\pm$ 0.015

Conversion: SI to traditional units—Blood ketones: 1 mmol/l $\approx$ 10.2 mg/100 ml.

high and were rising before breakfast. Table II shows the mean values ($\pm$ SEM) for the early and late injection regimens.

The acceptability of our methods to the children was determined by administering a simple questionnaire. Five of the nine children “enjoyed” participation and all found it “all right.” Seven of the nine preferred the tests to be performed at home rather than in hospital, and the other two had no preference.

Discussion

Our results show that precise metabolic data can be successfully collected from children at home, where the disruption of normal life inevitable with hospital admission can be minimised. They also show that a significant reduction in postprandial hyperglycaemia was obtained by giving the morning insulin injection 30 minutes before rather than immediately before breakfast (fig 1). This is most clearly seen when variation due to differences in fasting blood glucose concentrations is removed (fig 2). Confirmation that this reduction was due to the difference in injection time is given by the plasma insulin values (fig 3), which were significantly higher after the early injection from breakfast onwards. These higher insulin concentrations did not cause preprandial hypoglycaemia, however, and blood glucose concentrations before breakfast were stable or rising, probably because of insulin deficiency.

There was a wide variation in endogenous insulin secretory capacity, as shown by the variability of plasma C-peptide concentrations (fig 4). The similarity in mean C-peptide concentrations suggests that the maximal endogenous insulin response occurred with both injection regimens. Varying the injection time between 30 and five minutes before breakfast had no significant effect on the concentrations of the intermediate metabolites lactate, alanine, and pyruvate, which remained mainly within the normal limits for healthy adults.³ Fasting blood ketone concentrations were abnormally high, probably because of insulin deficiency, and returned to normal at the same time after breakfast on both injection regimens.

We have shown that, for diabetic children with varying endogenous insulin secretory capacity, giving the morning insulin injection before washing and dressing rather than afterwards can significantly reduce subsequent postprandial hyperglycaemia.

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