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Twenty-four-hour metabolic profiles in diabetic children receiving insulin injections once or twice daily

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Summary and conclusions

Twenty-four-hour metabolic profiles were performed twice in each of 15 diabetic children, once when they were receiving single daily injections of insulin (Monotard plus Actrapid) and once on a twice-daily regimen (Semitard plus Actrapid). Before the study control was optimised at home on each regimen. There were no differences in overall 24-hour diabetic control on the two regimens as measured by mean blood glucose concentration, area under the blood glucose curve, M value, and 24-hour urinary glucose excretion. Hyperglycaemia after breakfast occurred on both regimens. Significant differences were noted before breakfast, when blood glucose and ketone concentrations were lower and plasma free insulin higher on the single-injection regimen, and after supper and during the night, when blood glucose values were lower on the two-injection regimen and associated with a rise in plasma free insulin after the evening injection. Once-daily injections provided insufficient circulating insulin after the evening meal, while twice-daily injections did not last through the night. Plasma C peptide, indicating residual endogenous insulin secretion, was just detectable in two children but easily detectable in four children, whose 24-hour diabetic control was significantly better than that in the remaining 11 children.

Conclusions about the superiority of one insulin regimen over another must be based on specific differences in diabetic control. Both regimens studied achieved adequate control, and though neither provided physiological control specific modifications to the regimens could help to produce more normal profiles.

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Introduction

There has been much debate whether diabetic patients, both children and adults, should be given insulin once a day or more often. Arguments have been based on several findings and assumptions, including the clinical observation that patients poorly controlled or unstable on a single-injection regimen improve when switched to twice-daily injections.[1] Other retrospective studies relating long-term complications to poor diabetic control have suggested that patients given multiple daily injections have fewer complications than those on once-daily injections.[2] A prospective study in adults showed reduced progress of retinopathy on multiple injections compared with single-injection treatment.[3 4] Furthermore, on physiological principles, the normal pattern of circulating insulin can be more closely mimicked by more than one injection of insulin a day.[5] The findings in adults may not necessarily apply to children, however, because of the greater lability of diabetic control related to variations in growth, exercise, and emotion and to puberty. It has also been suggested that endogenous insulin production may play a greater part in diabetic control in children than in adults.[6]

Most studies comparing different insulin regimens have been limited by imprecise means of assessing diabetic control, such as random urine or blood testing. They have also failed to treat each regimen similarly in the effort devoted to achieving optimal control. Also, few studies have compared diabetic control on highly purified insulin regimens in children or adults. "Monocomponent" and "rarely immunogenic" insulins may have different durations of action from equivalent unpurified

preparations as they are less likely to be associated with circulating anti-insulin antibodies.[7] We used inpatient 24-hour metabolic profiles to study a group of diabetic children optimally controlled at home on both once- and twice-daily monocomponent insulin regimens.

Patients and methods

Fifteen insulin-treated diabetic children (seven boys, eight girls), with a mean age of 13·6 years (range 9·2-15·5 years), were studied (table I). They all attended the Oxford paediatric diabetic clinic and were emotionally stable and co-operative. They had had diabetes for a mean of 4·3 years (range 0·7-10·8 years). All the girls and five of the boys had entered puberty. Four of the girls and three of the boys were more than 10% overweight for their height.[8] Both parents and children gave their consent to the studies and the hospital ethics committee approved the investigation.

All the insulins used were porcine monocomponent. The once-daily regimen was a mixture of long-acting Monotard insulin (Novo, monocomponent lente) and short-acting Actrapid insulin (Novo). The twice-daily regimen was a mixture of medium-acting Semitard insulin (Novo, monocomponent semilente) and Actrapid insulin (Novo).

The study was designed as a randomised cross-over trial so that each child was studied twice, once on each regimen. Before both inpatient studies control was optimised at home over a mean of eight weeks (range 3-22 weeks) according to frequent (3 or 4 times daily) urine Clinitest estimations using the "two-drop" method[9] (two drops of urine to 10 drops of water, allowing estimation of urinary glucose concentration up to 278 mmol/l (5 g/100 ml)); fractional 24-hour urine glucose collections[10] (timed urine collections over the day with estimation of total glucose in each aliquot); and a series of glucose estimations performed on blood collected before each main meal on a selected day. The results of these home tests were used to modify the dose and ratios of the insulin regimens. When necessary the preprandial blood glucose estimations were repeated. After this sequence patients were considered optimally controlled on that particular regimen. The mean insulin dose at the time of the hospital study is shown for each regimen in table I. The interval between completing home testing and starting the hospital study was two to three weeks.

Patients were admitted to hospital on Friday evenings. An Abbocath 18-G Teflon intravenous cannula was inserted the next morning and a saline-filled syringe with a three-way tap attached. This system allowed the children to move their arms and move about freely. Insulin injections were given 15 minutes before breakfast and, during the twice-daily regimen, before the evening meal. Diet was carbohydrate-controlled and designed to mimic each child's usual diet at home. Children were encouraged to exercise at similar times and to a similar degree as they usually did at home and at school. The 24-hour protocol for blood sampling, meals, and injection times is shown in fig 1. Blood sampling was more frequent around meal times.

From each blood sample 1 ml was added to a pre-weighed tube containing 5 ml of 5% perchloric acid (PCA) to precipitate protein and 3 ml was added to a lithium heparin tube. PCA tubes were maintained at 4°C for up to 36 hours before neutralisation of the supernatant with 20% potassium hydroxide. Glucose and β-hydroxybutyrate concentrations were measured in the neutralised samples using enzymatic methods.[11] The hexokinase method was used for the glucose estimation. Lithium heparin samples were separated at 4°C within one hour of collection, the plasma stored at −20°C, and free insulin and C-peptide concentrations measured. Plasma free insulin was estimated by precipitation of insulin antibody and antibody-bound insulin with polyethylene glycol (PEG) 25% w/w at 37°C[12] and a charcoal separation radioimmunoassay.[13] Anti-insulin serum, GP8, was kindly supplied by Dr P Sönksen. Human monocomponent insulin standard was supplied by Novo Industri A/S, Copenhagen, and ^{125}I-labelled insulin by the Amersham Radiochemical Centre. Plasma C peptide was estimated by assay of C-peptide immunoreactivity and subtraction of the estimated contribution by antibody-bound pro-insulin. Plasma C-peptide immunoreactivity was estimated by a modified charcoal-separation radioimmunoassay,[14] using C-peptide antibody (M1230), human C-peptide standard, and ^{125}I-labelled C-peptide kindly supplied by Dr Lisa Heding of the Novo Research Institute, Copenhagen.

Urine volumes were recorded and urinary glucose concentration determined with an Analox glucose analyser using glucose oxidase. Statistical comparisons were performed on paired data using the Wilcoxon rank sum test.[15]

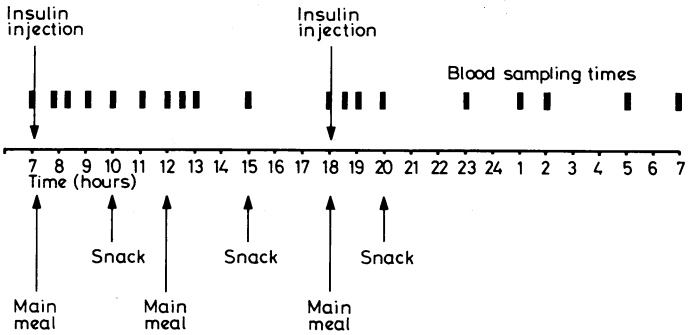

FIG 1—24-hour protocol for hospital study.

TABLE I—*Clinical details of children studied*

Case No	Sex	Age (years; decimals)	Duration of diabetes (years; decimals)	Puberty staging (breast and pubic hair according to Tanner)	Insulin dose (units) at time of study: Single injection Total	Single injection per kg	Two injections Total	Two injections per kg	Maximum plasma C-peptide (nmol/l)
1	M	13·3	2·3	3	72	1·3	70	1·4	0·19
2	F	15·5	1·3	4	68	1·1	64	1·1	0·40
3	F	14·6	6·8	2-3	58	1·1	82	1·5	0
4	F	14·1	1·7	4	212	3·5	200	3·2	1·04
5	M	11·1	1·7	1	68	1·7	64	1·6	0
6	M	13·8	4·6	3	46	1·0	40	0·9	0·08
7	M	12·4	2·1	2	42	0·9	60	1·4	0
8	F	15·3	10·9	4	90	1·4	122	1·8	0
9	F	15·1	5·3	4-5	60	1·0	78	1·3	0
10	F	13·6	1·1	3-4	28	0·5	30	0·6	0·90
11	F	15·1	2·6	3	118	2·1	120	2·3	0
12	M	13·9	9·2	3-4	70	1·4	72	1·4	0
13	M	13·6	0·7	3	36	0·8	40	0·8	0·32
14	F	13·8	9·8	2-3	48	1·3	58	1·5	0
15	F	9·2	3·7	1	38	1·2	42	1·3	0
Mean		13·6	4·3		71	1·4	76	1·5	

Results

Blood and urine glucose measurements: home v hospital—Neither the mean home blood glucose concentrations nor the mean 24-hour urinary glucose excretion were significantly different from those measured at the corresponding times in hospital (table II).

24-Hour metabolic control—Mean overall control of blood glucose on both injection regimens is shown in table III in terms of 24-hour mean blood glucose; area under the blood glucose curve; the M value[16]

(using all blood glucose measurements with 4·5 mmol/l (81 mg/100 ml) as the reference standard)—a mathematical expression describing a deviation from a reference ideal blood glucose value; and 24-hour urinary glucose excretion. In each case the smaller the value the better the diabetic control in terms of blood glucose concentration. Using these four methods of analysis there were no significant differences in mean diabetic control between the two regimens.

Blood glucose—Fig 2 shows the 24-hour mean blood glucose profiles on both once- and twice-daily regimens. The mean 24-hour profiles were abnormal on both regimens compared with those in normal young adults.[14] In particular, there was a wide range of blood glucose values over the daytime period on both regimens (4-16 mmol/l (72-288 mg/100 ml)). There were pronounced postprandial peaks, especially after breakfast, reaching the daily mean maximum level at 0900 on the single-injection regimen (14·5 mmol/l (261 mg/100 ml) and at 0815 on the two-injection regimen (16·3 mmol/l (294 mg/100 ml)). All values among normal young adults lay between 4 and 6·5 mmol/l (72 and 117 mg/100 ml). The profiles were similar on the two regimens except at: (*a*) 0700 and 0745, when the mean blood glucose concentration was lower on the one-injection regimen; (*b*) 2000 and 2300, when the mean blood glucose concentration was lower on the two-injection regimen; (*c*) 0100 and 0200, when the mean blood glucose concentration was lower on the two-injection regimen. While profiles varied between individual children, the patterns on the two regimens were similar in each child, except in two (cases 4 and 9), whose blood glucose values were consistently lower on the two-injection regimen. Blood glucose values of less than 3 mmol/l (54 mg/100 ml) were recorded between 2300 and 0500 (without symptoms of hypoglycaemia) in three of the 15 children while on the single-injection regimen and in 10 of the 15 children while on the two-injection regimen. From 0200 to 0700 mean blood glucose values rose significantly more on the two-injection regimen (4 to 9·1 mmol/l (72 to 164 mg/100 ml)) than on the single-injection regimen (5·7 to 7·8 mmol/l (103 to 141 mg/100 ml); $p<0·01$).

TABLE II—*Comparison of mean (±SD) home and hospital blood glucose and 24-hour urinary glucose estimations in children who required less than 10% change in insulin dose after home blood or urine testing*

	Single-injection regimen		Two-injection regimen	
	Home	Hospital	Home	Hospital
Blood glucose (mmol/l):				
Before breakfast	7·9±4·2 (n=10)	7·5±3·8*	10·6±2·0 (n=9)	11·0±5·0*
Before midday meal	4·7±2·7 (n=8)	4·7±3·9*	8·2±5·5 (n=8)	5·2±3·2*
Before evening meal	4·7±2·2 (n=9)	4·3±1·2*	5·3±2·6 (n=7)	4·7±1·7*
24-hour urinary glucose (mmol/l)	91±114	81±94	75±70	57±56

*Not significant.
Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml. Urinary glucose: 1 mmol/24 h ≈ 0·18 g/24 h.

TABLE III—*Mean 24-hour control (±SEM) on once- and twice-daily insulin regimens compared by four different methods*

	Single injection	Two injections
24-hour mean blood glucose (mmol/l)	8·2±0·6	8·2±0·7†
Area under blood glucose curve (mmol/l)	182·9±12·2	169·7±13·9†
M value*	57·8±9·2	69·7±13·0†
24-hour urinary glucose excretion (mmol)	67±21	67±22†

*Schlichtkrull.[16] †Not significant.

Plasma free insulin—The mean (±SEM) 24-hour plasma free insulin profiles were abnormal on both regimens (fig 3). In particular, mean fasting levels (12·9, 8·9 mU/l) were higher than normal (5·3±1·1 mU/l). The wide swings that occur in normal subjects in response to meals were not seen on either regimen. Peak levels on both regimens occurred three-and-a-half to four hours after breakfast (28-31 mU/l), while in normal subjects there was a peak of similar magnitude within 30 minutes of breakfast. The profiles were similar on the two regimens except for the initial and final samples, when the mean plasma free insulin level was significantly lower on the two-injection regimen ($p<0·05$, $p<0·01$ respectively). The plasma free insulin profile on the two-injection regimen could be divided into two component curves, corresponding to the morning and evening injections. There was a statistically significant ($p<0·05$) rise in mean plasma free insulin from 1800 to 2000, after the evening injection, followed by a fall in mean blood glucose concentration (fig 2). On the single-injection regimen the apparent rise in plasma free insulin from 1800 to 1900, after the evening meal, was not significant and was not associated with a fall in mean blood glucose (fig 2). There was a trend indicating that those children with the greater rise in blood glucose from 0100 to 0700 on the two-injection regimen also showed the greater fall in plasma free insulin levels over that time, but this was not statistically significant.

Plasma C peptide—Six of the 15 children had detectable levels of plasma C peptide (table I). Maximum plasma C peptide responses (highest levels recorded) were similar on the two regimens for each of the six children though they varied between children. In two of the six children maximum concentrations of plasma C peptide were 0·08 and 0·19 nmol/l, while in the four other children maximum concentrations ranged from 0·32 to 1·04 nmol/l. These four children were classed as C-peptide producers. The normal adult range is 0·37 (fasting) to 2·54 nmol/l in response to an oral glucose load.[17] In the four C-peptide producers mean blood glucose concentrations over the day ranged from 4·5 to 10·5 mmol/l (81-189 mg/100 ml), on the single-injection regimen, and from 3·0 to 10·2 mmol/l (54-184 mg/100 ml) on the two-injection regimen (fig 4). In the remaining 11 children mean blood glucose values ranged from 4·5 to 16·3 mmol/l (81 to 294 mg/100 ml) on the single-injection regimen and from 4·0 to 18·7 mmol/l (72 to 337 mg/100 ml) on the two-injection regimen (fig 4). On both regimens the mean blood glucose peaks reached after breakfast by those who produced no or only low C-peptide concentrations (16·3, 18·7 mmol/l (294, 337 mg/100 ml)) were significantly higher than those reached by the C-peptide producers (9·2, 10·2 mmol/l (166, 184 mg/100 ml); $p<0·05$). The four C-peptide producers had significantly lower mean M values than the remaining children on both regimens ($p<0·01$).

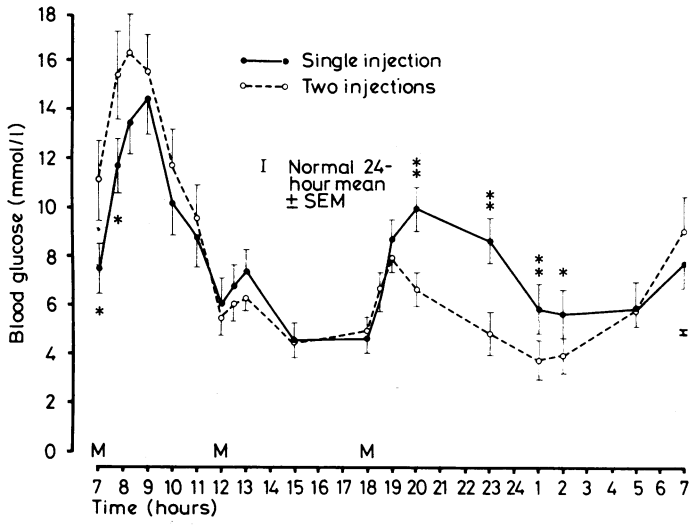

FIG 2—Mean 24-hour profiles of blood glucose (±SEM) on once- and twice-daily insulin regimens (n=15). M=Meal. *$p<0·05$; ** $p<0·01$.
Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

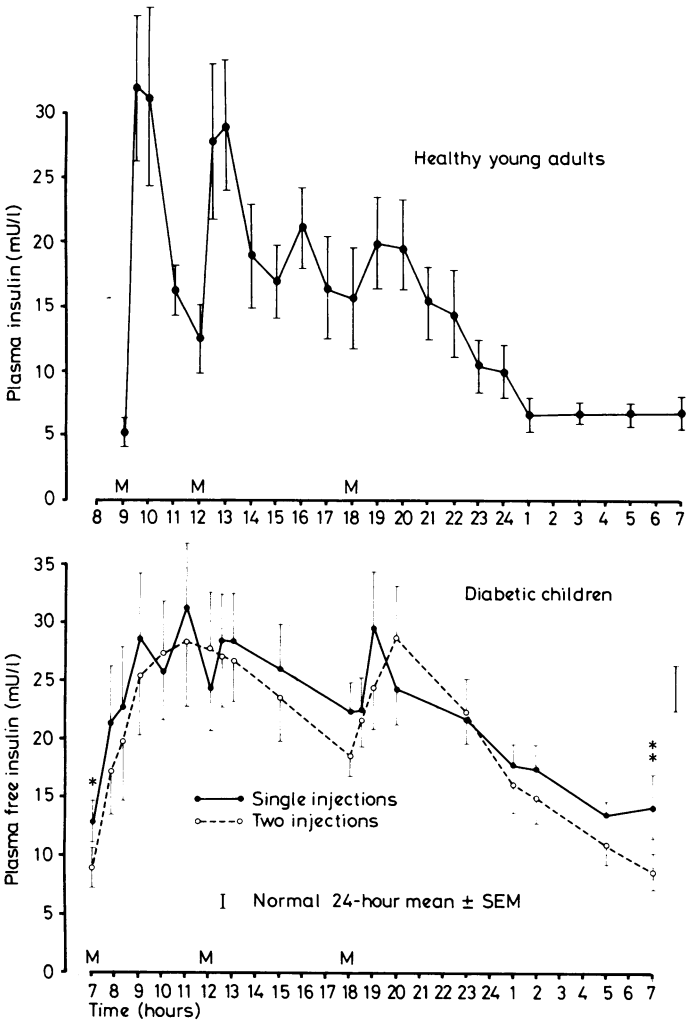

FIG 3—Mean (±SEM) 24-hour profiles of plasma insulinin eight normal young adults (top) and 15 diabetic children on once- and twice-daily insulin regimens (bottom). M=Meal. *p<0·05; **p<0·01.

Blood ketones—The 24-hour mean blood concentration of β-hydroxybutyrate on both regimens was significantly higher than mean total blood ketones in normal young adults[18] ($p < 0·01$ and $p < 0·05$ for the single- and two-injection regimens respectively; fig 5). Mean blood concentrations were similar from midday to 0200 on the two regimens. Concentrations were significantly higher on the two-injection regimen at 0500, 0700, and 0815. Concentrations at 0700 on the two-injection regimen were inversely related to plasma free insulin levels at that time ($r = 0·72$; $p < 0·01$).

Discussion

In this study comparing specific once- and twice-daily insulin regimens diabetic control in each of 15 children was assessed precisely over 24 hours under standardised conditions. Prior optimisation of control at home meant that each regimen was treated equally in terms of the effort devoted to achieving control. Mean home blood glucose values and 24-hour urinary glucose excretion were not significantly different from those measured in hospital. Though there was some individual variation, this suggests that differences from the home situation were minimised. The mean blood glucose profiles on both regimens differed from the normal in a manner similar to that in earlier adult studies.[19 20] Postprandial rises were greatest after breakfast. After the morning insulin injection and breakfast peripheral plasma free insulin levels on both regimens were slower to rise than in normal young adults[14] and insulin deficiency appeared greatest at this time, with a delay of one and a half to two hours before levels were high enough to reduce blood glucose concentrations. The normal maximum plasma insulin peak is after breakfast,[21] as hepatic gluconeogenesis and glycogenolysis are switched off in the transition from the fasting to the fed state.

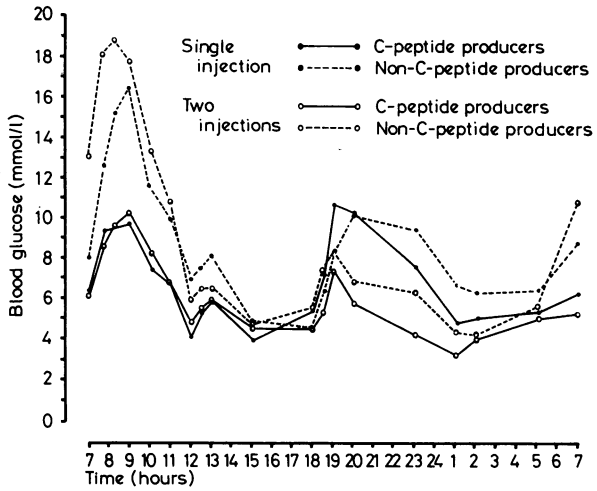

FIG 4—Mean 24-hour profiles of blood glucose for C-peptide producers (n=4) and non-C-peptide producers (n=11) on once- and twice-daily insulin regimens.

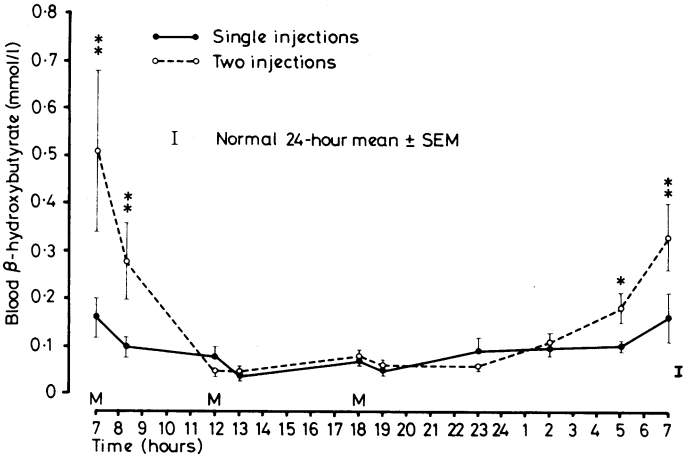

FIG 5—Mean (±SEM) 24-hour profiles of blood β-hydroxybutyrate on once- and twice-daily insulin regimens (n=15). M=Meal. *p<0·05; **p<0·01.

Conversion: SI to traditional units—β-Hydroxybutyrate: 1 mmol/l ≈ 10·4 mg/100 ml.

Mean overall diabetic control in terms of blood glucose concentrations showed no significant difference on the two regimens. There were, however, differences in the patterns of the mean blood glucose profiles between 2000 and 0200 (when the blood glucose concentrations were significantly lower on the two-injection regimen) and at 0700 (when the blood glucose concentrations were significantly lower on the single-injection regimen). The lower mean blood glucose value on the two-injection regimen at 2000 and 2300 was associated with a significant increase in plasma free insulin after the evening injection. The greater rise in blood glucose concentration from 0200 to 0700 and the higher 0700 mean blood glucose concentration on the two-injection regimen were associated with a lower mean plasma free insulin at 0700. Morning hyperglycaemia may result from rebound after overnight hypoglycaemia (Somogyi),[22] but insulin deficiency, rather than the Somogyi effect, may account for many apparent cases of this phenomenon[24 24] and may explain our findings on the twice-daily regimen. Compared with normal young adults, mean 24-hour

β-hydroxybutyrate concentrations were raised on both regimens, probably related to periods of insulin deficiency.[18] Significant differences in blood β-hydroxybutyrate patterns occurred from 0500 and 0815, when values were higher on the two-injection regimen, corresponding to a time of higher blood glucose and lower plasma free insulin levels.

Six of the 15 children had detectable concentrations of plasma C peptide. The features of these children were similar to those described in earlier studies.[25,26] Four of these six children, who were diagnosed as diabetic less than two years before the study, had higher C-peptide values than the two children diagnosed more than two years before study. Diabetic control, measured by the M-value, was better on both insulin regimens in the four C-peptide producers than in the low or non-producers of C peptide. This is also consistent with others' findings,[25,26] and suggests that endogenous insulin secretion may play a part in maintaining diabetic control in children.

Our findings contrast with previous 24-hour studies in children in which two daily injections of insulin have produced lower overnight and early morning blood glucose and ketone concentrations than one daily injection.[27,28] The single-injection regimen in both these earlier studies was lente, a conventional (not highly purified) beef insulin containing crystalline and amorphous zinc particles in the same ratio as Monotard. The twice-daily regimens were semilente, biphasic, or isophane insulin. In these earlier studies there was no attempt to optimise control on either regimen before the 24-hour study, and short-acting insulin was used only as a component of Rapitard. Sterky[28] studied children once only on their current regimen at that time, while most of Åkerblom's patients were studied first on their normal once-daily regimen and then restudied after stabilisation on to a similar dose on the twice-daily regimen.[28] Both these studies, therefore, failed to treat the once- and twice-daily regimens equally or achieve optimal control on either regimen. The failure of the single-injection regimen to provide adequate insulin for a 24-hour period in these two studies may simply have been due to inadequate dosage. The only previous study using monocomponent insulin in children was a non-randomised comparison of two twice-daily regimens by Winkler *et al* in 1977.[24] Children in whom twice-daily Semitard was associated with overnight hyperglycaemia (mean fasting blood glucose above 16 mmol/l (288 mg/100 ml)) showed improved control on a twice-daily regimen of Monotard and Actrapid (in ratio of 2:1). A statement that diabetic control on twice-daily monocomponent insulin was better than that on once-daily monocomponent insulin was not supported by any evidence.

By conventional standards,[29] mean diabetic control achieved in our study could be considered adequate on both regimens. Neither regimen, however, provided physiological diabetic control. While injected Monotard probably has a long enough duration of action to be given once daily, Semitard may not be suitable for a twice-daily insulin regimen. Rational modifications to both regimens might include a longer delay (20-30 minutes) between the morning injection and breakfast to allow higher circulating insulin levels after breakfast.[30] The carbohydrate content of breakfast could also be reduced, with a larger lunch allocation instead. Furthermore, a second small dose of Actrapid insulin could be added before the evening meal when using Monotard and Actrapid before breakfast. This would produce a regimen similar to that described by Phillips *et al*,[31] when ultralente was used once daily to provide "basal" insulin requirements and Actrapid was given morning and evening to cover meals.

Conclusions on the superiority of one insulin regimen over others must be based on objective and specific differences in diabetic control rather than on subjective clinical impression. Therefore, generalisations cannot be made about all once- or twice-daily insulin regimens. In this study of diabetic children comparing once-daily Monotard and Actrapid insulin and twice-daily Semitard and Actrapid insulin there were some specific differences in metabolic profiles but no overall differences in 24-hour diabetic control.

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