24-hour metabolic profiles in diabetic children

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SUMMARY 15 metabolic profiles were performed on 10 diabetic children who were on once-daily injections of insulin. Blood and urine glucose concentrations were high throughout much of the day and night, and were associated with abnormal levels of blood ketones, lactate, and pyruvate. The plasma free-insulin profiles gave a characteristic pattern for each type of insulin. The investigation gives valuable information for the clinical management of such children.

The importance of good diabetic control in the prevention of microvascular complications of diabetes has been stressed.¹ This applies as much to children as adults, although such complications during childhood itself are rare.² Although the importance of control is acknowledged, the clinical evaluation of control remains difficult and relies mainly on measurements of urinary glucose concentration made at home. However, reports stress the difficulties of defining diabetic control in these terms, and illustrate the disparity that can exist between random urine glucose and blood glucose measurements.³ It has also been shown that occasional blood glucose measurements correlate poorly with continuously monitored blood glucose⁴ and 24-hour profiles of blood glucose based on frequent intermittent samples.⁵ Furthermore, Alberti *et al.*⁶ showed that disturbances of intermediary metabolism can occur in apparently well controlled diabetic adults if abnormal diurnal patterns of blood lactate, ketones, and other metabolites exist in association with relatively normal blood glucose profiles.

We have attempted to examine the state of diabetic control of children by these methods. We performed 15 inpatient metabolic profiles and simultaneous fractionated urine collections⁷ on a selected group of diabetic children on various insulin regimens. The results were used to assess the quality of diabetic control and illustrate the pattern of action of different insulin regimens.

Patients and methods

15 metabolic profiles were performed on 10 co-operative diabetic children who were aged between 10.2 and 16.9 years (mean 13.6) at the time of the study. Consent was obtained both from the children and their parents before their admission to hospital: the study was accepted by the hospital's Ethics Committee. All the children were on once-daily injections of Lente*, Rapitard†, or Monotard† insulin. Further details of the patients are given in Table 1. Four children (Cases 1-4) were studied on both Lente and Rapitard insulins and Case 1 was also subsequently studied on Monotard insulin.

The clinical assessment of control in children attending the Oxford Paediatric Diabetic Clinic has been based on the patient's symptoms, growth velocity, and the 24-hour glucose excretion measured at home. In addition, measurements of urine glucose concentration, using the Clinitest 2-drop method,⁸ were performed at home two or three times daily. The outpatient assessment of the patients' control at the time of the study is shown in Table 1. All the patients were free from symptoms and excessive glycosuria (persistent home urine tests of 2% or greater), and were growing at a normal rate.

The protocol of the investigation is shown in Fig. 1. The children were admitted to hospital in the evening and the study began before breakfast the next morning. During the period in hospital the patient's dose of insulin and diet were continued as prescribed at home. The diet was prescribed in terms of carbohydrate with 25% of the total allowance at each main meal, 5% at the midmorning snack, and 10% in the afternoon and at bedtime. The children were kept up and active throughout the day and had walks in the hospital grounds. A plastic cannula was inserted into a peripheral vein at 0600 hours, and

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Table 1 Details of patients at time of investigation. The most recent outpatient clinical assessment of control is also shown

Case	Sex	Age	Duration of diabetes (years)	Insulin	Make	Dose (units)	Clinical assessment of control
1	M	10.3	6.2	Lente	Unspecified	38	Fair
		10.3	6.2	Rapitard	Novo	38	Poor
		11.3	7.2	Monotard	Novo	44	Poor
2	M	11.5	2.4	Lente	Unspecified	46	Fair
		11.5	2.4	Rapitard	Novo	46	Good
3	M	15.2	6.6	Lente	Unspecified	56	Good
		15.3	6.7	Rapitard	Novo	56	Good
4	M	14.9	1.3	Lente	Unspecified	34	Variable
		14.9	1.3	Rapitard	Novo	34	Variable
5	F	16.8	10.8	Monotard	Novo	76	Good
6	F	14.1	8.8	Monotard	Novo	62	Good
7	M	13.6	1.0	Monotard	Novo	40	Poor
8	M	15.9	4.0	Monotard	Novo	88	Fair
9	M	12.8	6.0	Monotard	Novo	22	Good
10	F	14.3	0.1	Monotard	Novo	44	Good

24-hour profile

Protocol

Admitted after school on Friday

Study from Saturday 7:00 to Sunday 7:00

Samples	Time	Events
→	6:00	Cannula inserted
→	7:00	Insulin
→	7:15	Breakfast
→	10:00	Snack
→	12:00	Lunch
→	15:00	Tea
→	18:00	Supper
→	20:00	Snack
→		Sleep
→		
→		
→		
→	7:00	End study

Fig. 1 Summary of protocol of the investigation.

kept patent with heparinised saline. Blood samples were taken at times related to meals and at intervals during the subsequent night. In addition all urine passed was collected, the volume measured, and an aliquot was saved for glucose estimation by glucose analyser (Analox)*.

Blood samples were put into preweighed tubes containing 5% perchloric acid for analysis of blood glucose, lactate, pyruvate, aceto-acetate, and 3-hydroxybutyrate; subsequent assays were performed

*Analox Instruments Ltd., Oxford.

using the enzymatic methods described by Bergmeyer and Gawehn.⁹ Blood was also put into lithium heparin and the plasma fraction separated and stored at -20°C for analysis of free insulin. Insulin antibodies were extracted from the plasma using polyethylene glycol¹⁰ and the free-insulin was measured by radioimmunoassay using a charcoal separation method.¹¹

The results for each patient were plotted against the time of day, giving a 24-hour profile for each variable. Mean values were calculated for the day-time period from 0700 to 2100 hours, and for the night-time fasting period from 2100 to 0700 hours from the area under the curve.

The patients were divided into three groups according to their insulin regimen and a mean profile for each group was calculated. The urine glucose loss in g/hour was plotted against time.

Results

Glucose. Fig. 2 shows an example of a blood and urine glucose profile obtained from Case 3 on Lente

Fig. 2 An example of blood and urine glucose profile obtained from a patient (Case 3) on Lente insulin.

insulin. During the daytime his blood glucose varied between 7.6 and 14.4 mmol/l (137–259 mg/100ml) in response to meals, with a mean for the daytime period of 11.0 mmol/l (199 mg/100 ml). This was associated with heavy glycosuria after breakfast and the evening meal but not after the midday meal. Overnight the blood glucose was relatively constant in the range 4.5 to 4.9 mmol/l (81–89 mg/100 ml) from 0200 to 0700 hours.

The mean and ranges of blood and urine glucoses are shown in Figs 3, 4, and 5 for the patients on Lente, Rapitard, and Monotard insulins respectively.

The blood glucose profiles of patients on Lente insulin (Fig. 3) showed high blood glucose levels during the day with maximum values 30 minutes after meals, ranging up to 34.5 mmol/l (620 mg/100 ml). The mean blood glucose for these patients for the daytime period was 13.9 mmol/l (251 mg/100 ml)

Fig. 3 Mean and range of blood glucose and mean urine glucose values over 24 hours for the 4 children on Lente insulin.

Fig. 4 Mean and range of blood glucose and mean urine glucose values over 24 hours for the 4 children on Rapitard insulin.

Fig. 5 Mean and range of blood glucose and mean urine glucose values over 24 hours for the 7 children on Monotard insulin.

compared with the night-time mean of 8.2 mmol/l (148 mg/100 ml). By 0500 hours, none of the patients had a blood glucose higher than 5.9 mmol/l (106 mg/100 ml) and the mean was 5.2 mmol/l (92 mg/100 ml). Glycosuria was heaviest in the mid-morning and after the evening meal and there was a mean urinary glucose loss of 60 g during the day compared with 17 g overnight.

Patients on Rapitard insulin showed a mean blood glucose profile (Fig. 4) with little difference between the mean daytime and night-time levels. The lowest points of the profile were seen before the midday and evening meals, but the blood glucose reached levels up to 47.2 mmol/l (850 mg/100 ml) after meals with associated heavy glycosuria. A difference between day and night-time glycosuria was observed and there was a mean excretion of 47 g during the day compared with 17 g overnight.

The mean blood glucose profile from the 7 patients on Monotard insulin (Fig. 5) showed less variation during the day than from those on the two other regimens. The mean daytime blood glucose was 11.9 mmol/l (214 mg/100 ml) compared with the night-time mean of 10.9 mmol/l (196 mg/100 ml). Overall the blood glucose values were lower on Monotard than on the other two insulins, and one child was borderline hypoglycaemic for much of the day. The urine glucose excretion was also lower in this group and no particular peaks were apparent.

Plasma insulin. The mean and ranges of the plasma insulin profiles for the three groups of patients are shown in Figs 6, 7, and 8

The mean insulin profile from the 4 patients on Lente insulin (Fig. 6) showed the peak plasma level (19.6 mU/l) 3 hours after injection with a steady fall

Fig. 6 Mean and range of plasma free-insulin value from 4 children on once-daily Lente insulin.

Fig. 7 Mean and range of plasma free-insulin values from 4 children on Rapitard insulin.

Fig. 8 Mean and range of plasma free-insulin values from 5 children on Monotard insulin.

thereafter, reaching a basal level of 7 mU/l 22 hours after the injection.

The mean plasma insulin profile from the 4 patients on Rapitard insulin (Fig. 7) showed a peak level (22.6 mU/l) occurring within 1½ hours of the injection, presumably due to the fast-acting Actrapid component, followed by a rapid fall during the subsequent 2 hours. Thereafter there was a slower fall in circulating free insulin throughout the remainder of the 24-hour period.

Plasma insulin values were obtained on 5 patients on Monotard insulin (Fig. 8). The mean plasma insulin profile was similar to that in patients on Lente insulin, with a peak value (20.3 mU/l) 3 hours after injection and a steady fall thereafter.

Total blood ketones. The total blood ketones were calculated from the sum of the acetoacetate and 3-hydroxybutyrate values. The mean 24-hour profile and ranges for all 15 studies is shown in Fig. 9. The mean total blood ketone concentration was raised (0.52 mmol/l) before the morning insulin injection, compared with normal adults.⁶ It fell to normal after the midday meal and remained at a normal level until 2300 hours, thereafter the concentration increased overnight.

Blood pyruvate and lactate. Blood concentrations of lactate and pyruvate were similar to normal adult values⁶ for most of the day in all the patients studied, but the levels were abnormally high in some individuals especially after meals. The blood lactate and pyruvate levels tended to change together and the lactate/pyruvate ratio showed little variation. Mean and ranges for blood lactate, pyruvate, and total ketones are shown in Table 2.

Fig. 9 Mean and range of blood total-ketones from 15 children on the three different insulin regimens.

Table 2 Mean (and range) of all blood lactate, pyruvate, and ketones measurements for each patient during a 24-hour period

Case	Lactate (mmol/l)	Pyruvate (mmol/l)	Ketones (mmol/l)
1	1.13 (0.52-2.21) 0.92 (0.46-1.45) 1.15 (0.50-2.40)	0.12 (0.08-0.20) 0.10 (0.05-0.17) 0.11 (0.06-0.18)	0.15 (0.04-0.45) 0.34 (0.06-1.75) 0.12 (0.02-0.44)
2	1.09 (0.45-1.78) 0.90 (0.31-1.61)	0.11 (0.06-0.15) 0.11 (0.07-0.16)	0.07 (0.04-0.17) 0.06 (0.00-0.14)
3	1.07 (0.64-2.55) 0.99 (0.63-2.64)	0.07 (0.00-0.12) 0.19 (0.07-0.23)	0.11 (0.03-0.23) 0.17 (0.07-0.54)
4	1.16 (0.68-2.60) 0.87 (0.53-1.42)	0.09 (0.06-0.14) 0.10 (0.05-0.13)	0.67 (0.07-0.50) 0.27 (0.04-1.15)
5	0.66 (0.35-0.90)	0.06 (0.02-0.10)	0.07 (0.00-0.40)
6	1.09 (0.59-2.51)	0.10 (0.06-0.17)	0.18 (0.03-1.97)
7	1.17 (0.54-1.90)	0.07 (0.03-0.10)	0.30 (0.05-0.73)
8	0.90 (0.53-1.21)	0.06 (0.04-0.09)	0.05 (0.02-0.10)
9	1.77 (0.69-2.72)	0.09 (0.05-0.14)	0.13 (0.02-0.34)
10	1.40 (0.85-2.65)	0.13 (0.11-0.17)	0.07 (0.03-0.13)

Conversion: SI to traditional units—Lactate: 1 mmol/l $\approx$ 9.0 mg/100 ml. Pyruvate: 1 mmol/l $\approx$ 8.8 mg/100 ml. Ketones: 1 mmol/l $\approx$ 10.2 mg/100 ml.

Discussion

The need for improved techniques to monitor the control of diabetes has been stressed with the recognition that better control leads to fewer complications and an improved prognosis.¹ Although clinically evident diabetic complications are rare in childhood,² early changes of diabetic retinopathy can be seen in up to 14% of diabetic children,¹² and basement membrane thickening may be found in renal or muscle biopsies.¹³ Efforts have therefore been made to evaluate the quality of diabetic control. Monitoring of control by the frequent measurement of capillary blood glucose levels at home has been shown to improve the standard of control in some adult diabetics,¹⁴⁻¹⁵ but there are problems of practicality that make such measurements in children less acceptable. The level of haemoglobin A_{1c} has been reported to correlate with other measurements of diabetic control¹⁶ and may prove to be an important additional tool in the management of diabetes. In children, 24-hour fractionated urine collections for glucose excretion have proved useful in improving the quality of diabetic control.^{7 17} However measurements of the 24-hour profile of glucose and other intermediary metabolites in adult diabetics have shown that the latter may be disturbed even in the presence of good blood glucose control.⁶ Moreover, knowledge of the actual patterns of diurnal change in blood glucose associated with the use of particular insulins provides an improved basis both for understanding the results of urine tests and for further rationalising clinical management.

This study was designed to assess the acceptability and value of 24-hour metabolic profiles in diabetic

children. The children found the investigation acceptable: the insertion of the plastic cannula was tolerated well and, once positioned, it caused little discomfort and enabled samples to be withdrawn without difficulty and without waking the child at night.

The children were not all in a state of ideal diabetic control, nor was the degree of control comparable between patients but, despite this, the study gives useful information about individual patients and patient groups. The results show that children who appear to be in reasonable control using normal outpatient clinical criteria may have high levels of blood glucose for much of the day and night with correspondingly high 24-hour urinary glucose losses. It is particularly noteworthy that the postprandial peaks of blood glucose may be extremely high and be associated with short periods of heavy glycosuria which may be missed by routine home urine tests, conventionally performed before meals, in particular before breakfast and the main evening meal.

The postprandial glucose peaks were particularly pronounced in patients on Rapitard insulin, who had relatively low blood glucose levels before their midday and evening meals. Patients on Lente insulin, on the other hand, had their lowest blood glucose levels at 0500 hours. This agrees with clinical experience that attempts to treat daytime glycosuria in patients on Lente insulin by increasing the insulin dose may cause early morning hypoglycaemia, whereas in patients on Rapitard insulin, similar attempts are more likely to cause hypoglycaemia before meals during the day. Patients on Monotard insulin had smoother profiles, with similar mean blood glucose levels during the daytime and the night-time periods.

The plasma insulin levels showed the profiles resulting from single injections of long-acting insulin. The peak plasma level was achieved earlier with Rapitard insulin than with Lente or Monotard insulin. Lente and Monotard were associated with a slower rise followed by a gradual fall throughout the remainder of the day. Patients on Rapitard had a more constant level of insulin during the day and night after their early high levels had subsided. It is noteworthy that the range of plasma insulin measured at any time was large, even within groups of patients on the same insulin. However the shape of the insulin profile was similar in patients within each small group.

The total blood ketone concentrations remained within the normal range for young adults throughout the 24-hour period in only one child, but in no case was it outside the range all the time. High levels of blood ketones were usual before the insulin injection and breakfast, and fell rapidly thereafter. However,

many patients did not achieve normal levels of blood ketones until after the midday meal. This is in keeping with a state of relative insulin insufficiency in the prebreakfast hours corresponding to the duration of the insulin action falling short of 24 hours.

The abnormal levels of lactate and pyruvate which were observed, and the marked swings in their values, confirmed similar findings in metabolic profiles performed on adult diabetics.⁶ They illustrate the degree to which metabolic homeostasis is disturbed in diabetic children, although the actual explanation for these variations is uncertain.

This study shows the value of metabolic profiles in diabetic children by allowing variations in insulin type and dose to be objectively evaluated. It also gives preliminary information about the action of different insulin regimens as the patterns of the profiles were relatively consistent within the groups and allowed some comparisons to be made. While it can and should be argued that any metabolic pattern seen in a study performed in hospital is likely to be different from similar observations made on children in their homes, we nevertheless feel that the patterns of change provide useful information on which to rationalise clinical management.

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