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Prediction and management of nocturnal hypoglycaemia in diabetes

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SUMMARY Blood glucose measurements were made at 2200, 0200, and 0800h in 102 children with diabetes during a 24 hour planned admission to hospital. Nocturnal hypoglycaemia (<3·0 mmol/l) occurred in 24 of 71 (34%) children on twice daily insulin and in three of 31 (10%) children on once daily insulin. Predictive value modelling showed that a blood glucose concentration of less than 7 mmol/l at 2200h was the best predictor of nocturnal hypoglycaemia, with a sensitivity of 63%, specificity of 94%, and positive and negative predictive values of 83%. Blood glucose measurement at 0800h had no predictive value for nocturnal hypoglycaemia. The mean (SD) glycosylated haemoglobin concentration of children on twice daily insulin who had nocturnal hypoglycaemia was 55 (8) mmol HMF/mol Hb, which was significantly less than that of children on twice daily insulin who did not have hypoglycaemia (64 (11) mmol HMF/mol Hb) or those on once daily insulin (62 (11) mmol HMF/mol Hb). A controlled trial was then performed in which 29 children with diabetes who had a blood glucose concentration at 2200h of <7 mmol/l measured by Reflocheck were randomised into two groups, one of which received 10 g carbohydrate supplement and the other of which did not. Thirteen of the 14 children in the control group had hypoglycaemia at 0200h, whereas the snack prevented hypoglycaemia in 12 of 15 in the test group. Blood glucose values in the two groups at 0800h were similar. We conclude that bedtime glucose measurement in children on twice daily insulin is a useful predictor for nocturnal hypoglycaemia, which can be prevented by a small carbohydrate snack in those at risk.

Unrecognised nocturnal hypoglycaemia may be a widespread and important problem in children with diabetes and is certainly a phenomenon that is difficult to detect. Failure to recognise nocturnal hypoglycaemia in adults has been reported to lead to transient hemiparesis,[1] organic personality syndrome,[2] and a syndrome masquerading as senile dementia.[3] Attempts to identify individuals at risk have included the measurement of early morning blood glucose concentrations[4] or overnight urinary cortisol concentrations.[5] Recently, Pramming *et al* reported that nocturnal hypoglycaemia may be predicted with reasonable accuracy in adults with diabetes by the measurement of an evening blood glucose concentration at 2300h.[6]

Nocturnal hypoglycaemia in children with diabetes has been studied, but less than in adults.[7–9] A frequency of 10–19% has been reported in children treated with twice daily insulin,[8 9] and it has been claimed that one consequence of unrecognised nocturnal hypoglycaemia has been overtreatment with insulin.[7] The present study assessed the prevalence of nocturnal hypoglycaemia in a sample of children with diabetes and tested the value of bedtime blood glucose measurements as a predictor of nocturnal hypoglycaemia in children who eat and go to bed earlier than adults and who were treated with insulin once or twice daily. The effect of a small bedtime carbohydrate snack in preventing hypoglycaemia in those at risk was then evaluated in a controlled trial.

Conversion: for HbA_{1c} by electrophoresis, 1 mmol HMF/mol Hb=0·19%; for HbA_{1c} by column chromatography, 1 mmol HMF/mol Hb=0·21%.

Patients and methods

Patients. There were two phases: (1) the prevalence and prediction study, which took place from January 1983 to January 1984, and (2) the intervention study, which took place from January to August 1984. The subjects were children admitted to hospital for annual review of their diabetic control.

They were aged 3 to 16 years and all had had diabetes for more than one year. No child had symptoms of nocturnal hypoglycaemia and all were clinically well when admitted between 1000 and 1300h for a 24 hour stay in hospital. The admission helped to standardise the times of insulin injection and food intake and the amount of exercise taken. Carbohydrate intake followed the recommendations of the British Diabetic Association, with about 50% being rich in polysaccharides. The last food intake was 90 minutes before the bedtime blood sample was taken, which was collected at about 2200h. Further samples were collected at 0200h and 0800h. No child woke at 0200h due to blood sampling. Some children were studied in each phase.

Prevalence and prediction study
There were 102 children in the prevalence and prediction study. Seventy one were receiving twice daily insulin mixtures; 32 took Monotard/Actrapid (Novo) and 39 took Humulin Isophane/Soluble (Lilly). The daily total insulin dose was similar in the two groups, being 0·62–2·50 U/kg (mean 1·01 U/kg) and 0·40–1·54 U/kg (mean 0·93 U/kg), respectively. Thirty one took a long acting insulin or an insulin mixture once daily in a dose ranging from 0·25 to 1·35 U/kg (mean 0·90 U/kg).

Intervention study
There were 97 children in the intervention study. Twenty nine (30%) had a blood glucose concentration of <7·0 mmol/l at 2200h measured by Reflocheck (Boeringer, Mannheim). They were randomised into two groups: (1) the control group (10 boys and four girls), which received no carbohydrate supplement, and (2) the test group (nine boys and six girls), which received 10 g carbohydrate as soon as the low bedtime blood glucose result was known. Twenty one children received twice daily insulin and eight received single dose treatment in the morning. All children in both studies had a 20 g carbohydrate snack at 2015h and those on twice daily insulin had their evening dose 20 minutes before the main meal at 1715h.

Methods. Fingertip heparinised blood samples were taken from all children at 2200, 0200, and 0800h and stored at 4°C until analysed for glucose by the hexokinase method[10] later in the day. In the intervention study blood glucose concentration was also measured at the bedside by Reflocheck (Boeringer, Mannheim).

Glycosylated haemoglobin (HbA_{1c}) (normal range 29–39 mmol HMF/mol Hb) was measured in all children during admission by a colorimetric assay,[11] and mean HbA_{1c} concentrations in different groups were compared by Student's unpaired *t* test. For the purpose of this study nocturnal hypoglycaemia was defined as a blood glucose concentration of less than 3 mmol/l.

Results were analysed using the predictive value model,[12] employing the following definitions.

(1) Sensitivity: the proportion of children with nocturnal hypoglycaemia at 0200h with a blood glucose concentration less than a given value at 2200h.

(2) Specificity: the proportion of children without nocturnal hypoglycaemia at 0200h with a blood glucose concentration greater than a given value at 2200h.

(3) Positive predictive value: the proportion of children with a blood glucose concentration less than a given value at 2200h who also had nocturnal hypoglycaemia at 0200h.

(4) Negative predictive value: the proportion of children with a blood glucose concentration greater than a given value at 2200h who did not have nocturnal hypoglycaemia at 0200h.

Results

Prevalence and prediction study.

Twice daily insulin
The blood glucose concentration fell to less than 3·0 mmol/l at 0200h in 24 of the 71 children (34%). Ten of the children with hypoglycaemia had received Monotard/Actrapid mixtures and 14 had received Humulin Isophane/Soluble mixtures.

The positive predictive values of blood glucose concentrations of less than 5, 6, 7, 8, 9, and 10 mmol/l at 2200h for nocturnal hypoglycaemia at 0200h are shown in Table 1, from which it can be seen that the best predictor was a blood glucose concentration of less than 7 mmol/l at 2200h, which had both a positive and a negative predictive value of 83%, a sensitivity of 63%, and specificity of 94%. More explicitly, 18 children had a blood glucose concentration less than 7 mmol/l at 2200h, and of

Table 1 *Predictive value models for nocturnal hypoglycaemia at 0200h from different blood glucose concentrations at 2200h*

Blood glucose (mmol/l) at 2200h	*Sensitivity*	*Specificity*	*Predictive value*	
			Positive	*Negative*
<5	42	96	83	76
<6	54	94	81	80
<7	63	94	83	83
<8	75	81	69	87
<9	83	81	71	91
<10	92	74	65	95

these, 15 had a concentration of less than 3 mmol/l at 0200h. Fifty three children had a blood glucose concentration of more than 7 mmol/l at 2200h, and of these, nine had a concentration of less than 3 mmol/l at 0200h. The relation between the blood glucose concentration at 2200h and the change in blood glucose from 2200h to 0200h is shown in the Figure. In eight of the 24 children with nocturnal hypoglycaemia the blood glucose concentration at 0200h was less than 2 mmol/l. The mean (SD) blood glucose concentration at 0800h of the children who had nocturnal hypoglycaemia was significantly lower (10·0 (6·9) mmol/l) than that of those who had not (13·6 (5·9) mmol/l). Similarly, the mean (SD) HbA_{1c} concentration of the children with nocturnal hypoglycaemia was significantly less than that of those with no nocturnal hypoglycaemia (55 (8) *v* 64 (11) mmol HMF/mol Hb). The predictive value of blood glucose measurements at 0800h for nocturnal hypoglycaemia the previous night was no better than chance (results not shown).

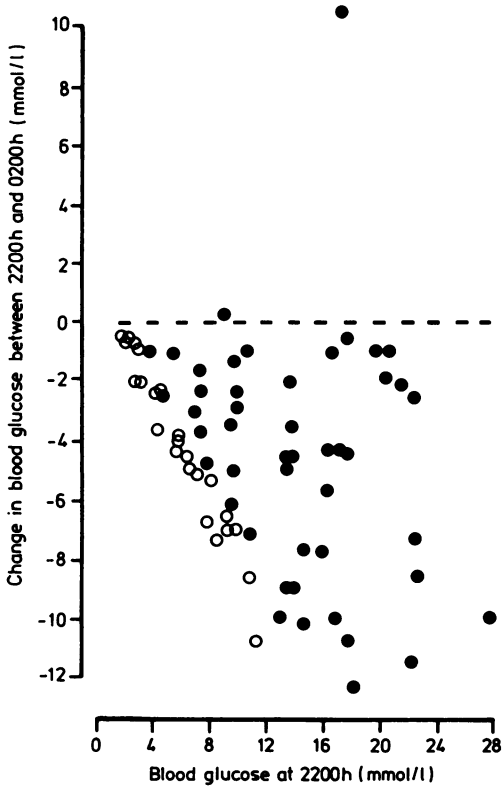

Figure *Blood glucose concentration at 2200h correlated with change in blood glucose between 2200h and 0200h in 71 children with diabetes taking twice daily insulin. Children with blood glucose concentrations of more than 3·0 mmol/l at 0200h are shown by solid circles and those with concentrations of less than 3·0 mmol/l at 0200h by open circles.*

Once daily insulin

Three of the 31 children who received once daily insulin developed nocturnal hypoglycaemia. The number was too small for comparison with those receiving twice daily insulin. The mean (SD) HbA_{1c} concentration of the 28 children who did not have nocturnal hypoglycaemia was 62 (11) mmol HMF/mol Hb, which was very similar to that of the 47 children on twice daily insulin who did not have nocturnal hypoglycaemia.

Glycosylated haemoglobin

There was no correlation between the blood glucose concentration at 0200h and the HbA_{1c} concentration in any subgroup or in the total study sample.

Intervention study. In all cases the laboratory measurement of blood glucose confirmed the Reflocheck estimate at 0200h of <7 mmol/l. The mean (range) of the laboratory determinations was 3·8 (1·6 to 6·0) mmol/l. Results were analysed, taking account of whether the children had insulin once or twice a day (Table 2).

Twice daily insulin

Ten of the 11 children in the control group had hypoglycaemia at 0200h, whereas only two of the 10 in the test group had a blood glucose concentration of <3·0 mmol/l at 0200h. The blood glucose concentration fell between 2200 and 0200h in every child in the control group, whereas the concentration rose in eight of the children in the test group, but one of these had hypoglycaemia at 0200h notwithstanding. By 0800h a similar mean rise in

Table 2 *Blood glucose concentrations at 2200h and change in blood glucose at 0200h and 0800h in children with diabetes at risk of nocturnal hypoglycaemia. Values are mean (SEM)*

Patient group	*(n=)*	*Blood glucose or change in blood glucose (mmol/l)*		
		2200h	*0200h*	*0800h*
Twice daily insulin				
Bedtime carbohydrate	(10)	3·2 (0·4)	+0·9 (0·4)	+7·9 (1·4)
No carbohydrate	(11)	4·0 (0·5)	−2·0 (0·4)**	+7·6 (2·6)
Once daily insulin				
Bedtime carbohydrate	(5)	3·8 (0·2)	+2·1 (1·3)	+3·5 (1·8)
No carbohydrate	(3)	4·8 (0·8)	−1·9 (0·6)*	+5·7 (0·7)
All patients				
Bedtime carbohydrate	(15)	3·4 (0·3)	+1·3 (0·5)	+6·3 (1·2)
No carbohydrate	(14)	4·2 (0·4)	−2·0 (0·3)**	+7·1 (1·9)

*p<0·05, **p<0·01 by Student's *t* test.

blood glucose concentration of 7–8 mmol/l had occurred in both groups, but the range of change was greater in the control patients, suggesting that a Somogyi effect might have occurred in some.

Once daily insulin

There were fewer patients taking insulin once daily, reflecting current clinical practice. There had been a fall in blood glucose concentration at 0200h in all three of the control patients, and two became asymptomatically hypoglycaemic. In all five test patients the blood glucose concentration had risen at 0200h. The mean rise in blood glucose concentration at 0800h in both groups was similar but less than that seen in patients taking twice daily insulin.

Glycosylated haemoglobin

The quality of diabetic control as reflected in the HbA_{1c} measurements ranged from 39 to 60 mmol HMF/mol Hb but was similar in all four subgroups, mean (SD) values (in mmol HMF/mol Hb) being 53 (6) in test patients on twice daily insulin, 47 (5) in control patients on twice daily insulin, 55 (3) in test patients on once daily insulin, and 52 (9) in control patients on once daily insulin.

Discussion

This project was designed to measure the prevalence of nocturnal hypoglycaemia in children with diabetes with minimum inconvenience under relatively standardised conditions, which were thought to favour hyperglycaemia rather than hypoglycaemia because of the relative inactivity associated with admission to hospital. A blood glucose concentration of 3 mmol/l was used as a working definition of hypoglycaemia based on previous work and 0200h was chosen as the sampling time because of the authors' previous experience in diabetic summer camps where most symptomatic hypoglycaemia occurred between 0100 and 0300h.

About one third of the children taking insulin twice daily experienced symptomatic nocturnal hypoglycaemia, and among these one third had severe hypoglycaemia with a blood glucose concentration of less than 2 mmol/l. In contrast, only one tenth of the children receiving insulin once a day experienced nocturnal hypoglycaemia. If the three subgroups, twice daily insulin with or without hypoglycaemia and once daily insulin without hypoglycaemia, were considered the quality of diabetic control judged by HbA_{1c} concentrations was indifferent to poor and was similar in the two subgroups without hypoglycaemia, whereas the patients experiencing hypoglycaemia had a significantly lower mean HbA_{1c} concentration, although there was no direct correlation between HbA_{1c} and blood glucose concentrations at 0200h within this subgroup. This is not surprising as the HbA_{1c} reflects long term overall glucose homeostasis and the measurement of blood glucose at 0200h took place on one night only. A legitimate inference is that patients with lower HbA_{1c} concentrations taking insulin twice daily are more prone to nocturnal hypoglycaemia. Should this cause concern or be regarded merely as an epiphenomenon? In favour of the latter view is that the children were clinically well at the time of study and the hypoglycaemia, by definition, was asymptomatic. Against this is the evidence that nocturnal hypoglycaemia in adults can damage the brain, and it is plausible to suggest that the effect is more likely to be gradual and cumulative rather than abrupt. Anecdotally, two of the children in the present study subsequently had transient hemiparesis and a third had early morning convulsions, all as complications of nocturnal hypoglycaemia. All three children had HbA_{1c} concentrations below 50 mmol HMF/mol Hb at the time and were perceived to have excellent diabetic control.

While this study may have fuelled the debate on what is optimal control for a child with diabetes without providing a clear answer to that question, it has also clarified ways in which nocturnal hypoglycaemia may be predicted. Analysis of bedtime and early morning blood glucose concentrations has shown clearly that a bedtime concentration of less than 7 mmol/l is a useful predictor that hypoglycaemia will occur. This is in keeping with the observation of Pramming *et al* that 80% of adults on twice daily insulin with a blood glucose concentration of less than 6 mmol/l at 2300h had nocturnal hypoglycaemia.[6] We were unable to find any association between nocturnal hypoglycaemia and subsequent blood glucose concentrations measured at 0800h, which contrasts with an earlier report.[8]

The simple intervention study confirmed that bedtime glucose monitoring with the Reflocheck overestimated blood glucose concentrations in the low and low-normal glycaemic range[13] but was none the less useful in predicting which children would experience nocturnal hypoglycaemia. More importantly, we have shown that this risk can be ameliorated by a 10 g carbohydrate snack without prejudice to the overall quality of diabetic control as reflected in the 0800h blood glucose reading. We think that this simple procedure is worth recommending to families for use at home, in particular in those cases where there may be cause to suspect that nocturnal hypoglycaemia is occurring in the child with diabetes.

Ideally, each child should have been studied on

more than one occasion and acted as a self control. We did not consider it justified to admit a child to hospital more than once and preferred to use a less elegant experimental model but one that was ethically more acceptable. Normal bedtime for the children in this study was from 2030 to 2200h, and the blood glucose testing and carbohydrate supplementation did not change this routine, but care was taken to ensure that those who had extra carbohydrate at 2200h cleaned their teeth.

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