provides an additional variable¹ for determining whether a particular fetus may have been affected and therefore for assessing the validity of any future presumptive antenatal test based on the study of amniotic-fluid cells or fetal blood.

We thank Miss G Dodds and Miss L Andruzzenko for excellent technical help. We are especially grateful to Mr I Rocker for providing material from control fetuses, and to Prof V Dubowitz and Dr R Harris for providing material from at-risk fetuses. This work was supported by a research grant from the Muscular Dystrophy Group of Great Britain.

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(Accepted 8 November 1979)

Detection of unrecognised nocturnal hypoglycaemia in insulin-treated diabetics

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Summary and conclusions

Cortisol to creatinine ratios in overnight urine samples, urinary glucose excretion, and plasma glucose concentrations were determined in 43 diabetic inpatients. All initially had normal cortisol to creatinine ratios ($<55 \times 10^{-6}$) and were initially treated by increasing their long-acting insulin component. Nine patients in whom this ratio became raised then had their long-acting insulin component reduced until their fasting plasma glucose concentration was 4-7 mol/l (72-126 mg/100 ml). The 34 patients who had never had a raised ratio were treated by increasing their long-acting insulin component until their fasting plasma glucose concentration was in the range 4-7 mmol/l. All the raised cortisol to creatinine ratios were clearly separate from the other values. A

mean reduction in total insulin dose of 23% and in long-acting insulin dose of 53% was achieved, abolishing presumptive nocturnal hypoglycaemia by reducing the ratio to normal and dramatically improving diabetic control.

Although there was no definite evidence that the patients who had raised cortisol to creatinine ratios had suffered from nocturnal hypoglycaemia, these results strongly support the view that a raised ratio indicates an otherwise unrecognised episode of this condition.

Introduction

In insulin-treated diabetes the occurrence of fasting hyperglycaemia may be due either to insufficient long-acting insulin to last the night or to overtreatment with insulin, which initially produces hypoglycaemia and then rebound hyperglycaemia.¹ It is important to distinguish between these two causes of morning hyperglycaemia so that an appropriate alteration in insulin dose can be made. Nocturnal hypoglycaemia may be recognised by the patient or his doctor, but clinical diagnosis may be difficult.² The definitive method of distinguishing between the two possibilities is frequent blood-glucose monitoring during the night; this, however, is not

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always practicable even in hospital, and the problems are greater in outpatients.

Frank nocturnal hypoglycaemia is accompanied by an increased cortisol to creatinine ratio in the early-morning urine specimen.³ We have therefore measured this ratio in insulin-treated diabetic inpatients in whom nocturnal hypoglycaemia was not suspected. The results were used as a guide to insulin dosage in controlling fasting blood glucose values.

Patients and methods

Forty-three insulin-taking diabetic inpatients (26 men, 17 women) aged 17-73 years co-operated in the study. All were continent, and the duration of diabetes ranged from two to 23 years. Most were recovering from an operation (mainly amputation), though some were in hospital for stabilisation of their diabetes. All were taking a carbohydrate-restricted diet, which included a snack at 10 pm. Throughout the trial the patients continued with their diets assessed by the dietitians. None of the patients had symptoms or signs suggestive of nocturnal hypoglycaemia.

The patients were studied for three to six days (mean five). After voiding urine at 10 pm they collected all their urine passed overnight; urine passed between 7 am and 12 noon was also collected. Blood for glucose measurement was taken at 7 am and 12 noon. Plasma glucose concentration, urinary glucose excretion, and urinary cortisol to creatinine ratios were measured daily, the cortisol to creatinine ratio being obtained by the early afternoon to permit alteration to treatment.

All patients entered the trial with normal cortisol to creatinine ratios³—that is, below 55×10^{-6} —and all were treated by increasing the long-acting component of their insulin dose—namely, the Lente, Monotard, or evening Isophane or Retard—in steps of about eight units. When the fasting plasma glucose concentration exceeded 12 mmol/l (216 mg/100 ml) the dosage was adjusted the same day, and when the concentration was 8-12 mmol/l (144-216 mg/100 ml) the dosage was adjusted on alternate days. Patients who never had a raised cortisol to creatinine ratio were treated in this way until the fasting plasma glucose concentration was 4-7 mmol/l (72-126 mg/100 ml). Any patient whose ratio exceeded normal, thus suggesting hypoglycaemia, had the dosage of the long-acting component reduced immediately by 10-20 units, and if the ratio was still high the next day a similar reduction was made. As in patients with normal ratios, the aim was to achieve a fasting plasma glucose concentration of 4-7 mmol/l.

Laboratory methods—Plasma glucose concentration was measured by a glucose oxidase method using an ANALOX glucose analyser, and urinary glucose excretion was determined with Clinitest tablets and an appropriate dilution of urine. In the overnight urine sample creatinine was measured by the Jaffe reaction⁴ and cortisol by a specific radioimmunoassay kit (Eurotope Services Ltd, London). Results with this kit are identical with those obtained with the competitive protein binding method⁵ (regression equation $y = 1.05x - 10$; $r < 0.986$, $p = 0.001$; $n = 40$). Advantages, however, are shorter incubation times and shorter counting times for ¹²⁵I-cortisol, which allow results to be produced within four hours. Statistical analysis was by Student's distribution or paired *t* test.

Results

Of the 43 patients, nine (group 1) had a raised cortisol to creatinine ratio detected at least once, and 34 (group 2) never had a raised ratio detected (table I). There was no significant difference between the groups in age, sex distribution, or types of insulin used. Both total insulin dose and dose/kg body weight, however, were significantly higher in group 1.

The dose of long-acting insulin was reduced in the nine patients with presumptive nocturnal hypoglycaemia; in five, however, a further raised cortisol to creatinine ratio was detected and a second dose reduction was necessary. The detection of a raised cortisol to creatinine ratio in the overnight urine sample coincided with increases in plasma and urinary glucose concentrations which fell after reduction of the insulin dose (table II). The figure shows the results in a typical case. Interestingly, the full benefits of reducing the insulin dose in group 1 were not achieved until the second day after dose reduction, and the second episode of presumptive hypogly-

TABLE I—Clinical details of patients in whom raised cortisol to creatinine ratio occurred at least once (group 1) and in whom raised ratio never occurred (group 2)

	Group 1	Group 2	p
No of patients	9	34	
Age range (years)	21-71	17-73	NS
Sex distribution	5M, 4F	21M, 13F	NS
Mean weight (kg) $\pm$ SE	75.3 $\pm$ 3.2	73.1 $\pm$ 1.9	NS
Mean total insulin dose (U) $\pm$ SE	74.7 $\pm$ 6.2	43.8 $\pm$ 2.9	$p < 0.001$
Mean insulin dose/kg (U) $\pm$ SE	1.01 $\pm$ 0.10	0.61 $\pm$ 0.04	$p < 0.001$
Initial insulin regimen (no of patients)			
Neutral and Retard (twice daily)	4	6	
I2S Lente (once daily)	2	5	
Monotard and Actrapid (once daily)		2	
Monotard and Actrapid (twice daily)	3	10	
Soluble and Isophane (twice daily)		4	
Monotard (once daily)		7	

NS = Not significant.

Plasma glucose concentration, urinary glucose excretion, and cortisol to creatinine ratio in typical patient with presumptive nocturnal hypoglycaemia. --- = Upper limit of normal range.

Conversion: SI to traditional units—Plasma glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Urinary glucose: 1 mmol $\approx$ 0.18 g.

caemia caused an even higher fasting plasma glucose concentration in five patients.

Patients in group 2 were treated by progressively increasing the long-acting insulin dose, and plasma and urinary glucose concentrations rapidly approached normal (table III). The cortisol to creatinine ratio did not change during this period.

Table IV shows the overall changes in long-acting insulin dosage and plasma and urinary glucose concentrations in the two groups. Patients in group 1 had a significantly higher initial dose of long-acting insulin ($p < 0.05$), though the final dose was significantly lower ($p < 0.001$). Nevertheless, in both groups the mean fasting plasma glucose concentration was significantly reduced to under 7 mmol/l and urinary glucose excretion was negligible at the end of treatment.

All the patients in group 1 required a reduction in their dose of long-acting insulin, and all showed considerable improvement in plasma glucose concentrations and urinary glucose excretion. Conversely, all the patients in group 2 required an increase in their dose of long-acting insulin to yield similar results. Table V gives the distribution of cortisol to creatinine ratios obtained in all 43 patients. Raised values were clearly distinct from the rest and were used as the basis for reducing the insulin dosage in group 1.

TABLE II—Plasma glucose concentrations, urinary glucose excretion, and urinary cortisol to creatinine ratios in group 1. Results expressed as means $\pm$ SE of mean and compared with corresponding result for previous night

	No of patients	Plasma glucose (mmol/l)		Urinary glucose (mmol)		Urinary cortisol: creatinine ($\times 10^{-6}$)
		7 am	12 noon	10 pm-7 am	7 am-12 noon	10 pm-7 am
Day before hypoglycaemia ..	9	13.4 $\pm$ 1.3	12.5 $\pm$ 1.1	52.1 $\pm$ 12.2	55.0 $\pm$ 12.2	20.2 $\pm$ 3.5
First episode of hypoglycaemia ..	9	15.7 $\pm$ 1.0*	15.9 $\pm$ 1.6*	104.3 $\pm$ 18.3*	118.8 $\pm$ 22.8*	172.3 $\pm$ 69.2†
Second episode of hypoglycaemia ..	5	18.1 $\pm$ 1.9*	15.8 $\pm$ 2.6†	128.8 $\pm$ 21.6†	123.2 $\pm$ 22.8*	170.0 $\pm$ 71.0†
Days after final reduction in insulin:						
One	9	10.4 $\pm$ 1.2†	9.8 $\pm$ 0.8†	47.7 $\pm$ 13.3†	56.1 $\pm$ 13.9†	30.2 $\pm$ 3.4†
Two	9	6.8 $\pm$ 0.5†	7.7 $\pm$ 0.5*	12.8 $\pm$ 3.9*	11.1 $\pm$ 2.8†	23.1 $\pm$ 3.9†

Statistical analysis was by paired *t* test. **p* < 0.05. †*p* < 0.01. ‡Not significant.

Conversion: SI to traditional units—Plasma glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Urinary glucose: 1 mmol $\approx$ 0.18 g.

TABLE III—Plasma glucose concentrations, urinary glucose excretion, and cortisol to creatinine ratios in group 2 receiving long-acting insulin. Results are expressed as means $\pm$ SE of mean and compared with corresponding results for previous day

Day of treatment	No of patients	Plasma glucose (mmol/l)		Urinary glucose (mmol)		Cortisol:creatinine ($\times 10^{-6}$)
		7 am	12 noon	10 pm-7 am	7 am-12 noon	10 pm-7 am
1	34	14.5 $\pm$ 0.6	16.4 $\pm$ 0.5	66.6 $\pm$ 6.7	55.6 $\pm$ 7.8	21.6 $\pm$ 2.1
2	34	11.4 $\pm$ 0.5*	10.4 $\pm$ 0.5*	38.9 $\pm$ 38.9*	27.8 $\pm$ 5.6*	21.1 $\pm$ 1.6†
3	34	8.5 $\pm$ 0.5*	8.0 $\pm$ 0.4*	13.9 $\pm$ 2.8†	11.1 $\pm$ 2.8*	23.9 $\pm$ 1.9†
4	17	7.4 $\pm$ 0.5*	7.0 $\pm$ 0.4*	5.6 $\pm$ 2.2*	5.6 $\pm$ 2.2*	24.0 $\pm$ 2.9†
5	9	6.5 $\pm$ 0.5*	6.1 $\pm$ 0.3*	5.6 $\pm$ 2.8†	5.6 $\pm$ 7.8†	19.4 $\pm$ 2.7†

Statistical analysis was by paired *t* test. **p* < 0.01; †*p* < 0.05.

Conversion: SI to traditional units—Plasma glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Urinary glucose: 1 mmol $\approx$ 0.18 g.

TABLE IV—Overall changes in long-acting insulin dosage, plasma glucose concentrations, and urinary glucose excretion in groups 1 and 2. Results are given as means $\pm$ SE of mean and ranges

			Group 1 (n = 9)			Group 2 (n = 34)		
			Mean	Range	P	Mean	Range	P
Long-acting insulin (U)								
Initial	..	..	32 ± 6.2	16-64	< 0.001	20 ± 2.2	0-42	< 0.001
Final	..	..	15 ± 4.7	0-40		35 ± 2.6	12-64	
7 am plasma glucose concentration (mmol/l)								
Initial	..	..	14.9 ± 3.1	10.2-19.8	< 0.001	14.5 ± 0.6	8.4-21.6	< 0.001
Final	..	..	6.9 ± 0.4	5.9-7.9		6.3 ± 0.2	4.1-8.4	
12 noon plasma glucose concentration (mmol/l)								
Initial	..	..	13.4 ± 1.1	9.8-18.1	< 0.01	16.4 ± 0.6	6.6-21.2	< 0.001
Final	..	..	7.7 ± 0.5	5.5-10.9		6.9 ± 0.3	4.4-9.4	
Overnight urinary glucose excretion (mmol)								
Initial	..	..	72.2 ± 9.4	22.2-111.0	< 0.001	66.6 ± 6.7	11.1-166.5	< 0.001
Final	..	..	11.1 ± 2.2	0-33.3		5.6 ± 2.2	0-44.4	
7 am-12 noon urinary-glucose excretion (mmol)								
Initial	..	..	66.6 ± 13.9	16.7-138.8	< 0.01	55.6 ± 7.8	5.6-210.9	< 0.001
Final	..	..	16.7 ± 6.1	0-61.1		8.3 ± 2.2	0-55.6	

Statistical analysis was by Student's *t* test.

Conversion: SI to traditional units—Plasma glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Urinary glucose: 1 mmol $\approx$ 0.18 g.

TABLE V—Distribution of cortisol to creatinine ratios in all urine samples from the 43 patients

Cortisol to creatinine ratio ($\times 10^{-6}$)	..	..	0-	5-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-	85-	90-	95-	>100
No of samples	..	..	3	17	25	29	29	20	12	12	8	4	2	2	2	2*	1*	1*	1*	1*	1*	1*	8*

*Long-acting insulin dose reduced after these samples were taken.

Discussion

There was no definite evidence that the nine patients who had raised cortisol to creatinine ratios in their overnight urine samples had suffered nocturnal hypoglycaemia. The essential point is that their diabetic control improved dramatically with reduction in insulin dosage, which also reduced the cortisol to creatinine ratio to normal. The patients with normal cortisol to creatinine ratios, however, showed reductions in plasma glucose concentrations and urinary glucose excretion after increases in their insulin dosage, and their ratios never became high.

We do not believe that these findings are a consequence of a beneficial effect of increased length of stay in hospital because, as table II and the figure show, this was not so in those whose

cortisol to creatinine ratios were still raised despite the first reduction in insulin dosage.

The patients with presumptive nocturnal hypoglycaemia received significantly higher total and long-acting insulin doses, though the mean insulin dose/kg body weight (1.01 U) was slightly less than that which produced hypoglycaemia in the Nottingham study (1.16 U).² Our patients had appreciable urinary glucose losses (tables II and V), which continued the day after reducing the insulin dose and were associated with unacceptably high plasma glucose concentrations. Only on the second day after reducing the dose did plasma glucose concentration and urinary glucose excretion fall to acceptable values, which shows the severity and duration of the metabolic disturbance after unrecognised nocturnal hypoglycaemia.

Our aims of abolishing glycosuria and producing fasting

plasma glucose concentrations of 4 to 7 mmol/l (72-126 mg/100 ml) were not achieved in all patients, because some left hospital before complete adjustment of their insulin dose had been made. Several patients still had unsatisfactory noon plasma glucose concentrations, indicating the need for additional "quick-acting" insulin in the morning.

In our study 21% of the patients suffered an episode of presumptive nocturnal hypoglycaemia, whereas Gale and Tattersall reported an incidence of 56%²; the comparable mean reductions in insulin dose required for good diabetic control were 23% and 25%. There is little information on the overall incidence of nocturnal hypoglycaemia in insulin-requiring diabetes, and both we and Gale and Tattersall² in some way selected the subjects for study.

Our results strongly support the view that measuring the cortisol to creatinine ratio in an overnight urine specimen is a useful detector of an otherwise unrecognised nocturnal hypoglycaemic event. The test is straightforward and may be performed on a specimen collected by any co-operative continent patient, including outpatients. It provides a simple means of detecting poor glucose regulation caused by overtreatment with insulin and yields clear separation of normal and abnormal results. As well as serving as a guide to insulin treatment, it may elucidate how overtreatment with insulin causes unstable diabetes.

Several causes of false-positive results, however, will probably be recognised with continued study; Cushing's syndrome would be one cause, as would severe depression and a major physical upset such as nocturnal pulmonary embolism.

We acknowledge the encouragement and advice of Dr P J R Phizackerley and financial support from the Oxford Area Health Authority Research Committee. We thank the housemen and ward staff who helped to collect the samples, and Mrs Jean Smith for preparing the manuscript.

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(Accepted 19 October 1979)

Ketotifen in adult asthma

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Summary and conclusions

The efficacy and adverse effects of ketotifen 1 mg twice daily and 2 mg twice daily were compared with placebo in 50 patients with atopic asthma in a multicentre, double-blind study. Ketotifen in the higher dosage caused a slight reduction in salbutamol usage and a modest improvement in breathing in patients not already receiving inhaled corticosteroids. The drug was ineffective in patients receiving inhaled corticosteroids. Drowsiness was a troublesome effect causing withdrawal from treatment or reduction of dosage in seven patients while receiving ketotifen compared with only three while receiving placebo.

This study was designed by Dr A J Dyson on behalf of a subcommittee of the Research Committee of the British Thoracic Association, whose members were: Drs Elizabeth A Hills (chairman), A J Dyson, J A R Friend, R Greenwood, A D Mackay, C Skinner, and P Smith. The study was co-ordinated and the report prepared by Dr A D Mackay, whose research fellowship was also supported by the Chest, Heart and Stroke Association.

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Thus the slight beneficial effect of ketotifen on asthma must be balanced against its side effect of drowsiness.

Introduction

Sodium cromoglycate benefits asthmatic patients.¹ Oral anti-allergic compounds that like cromoglycate inhibit anaphylactic mediator release in laboratory models have now been synthesised. These might benefit patients unable to use an inhaler efficiently. One of these compounds, ketotifen, is a benzocycloheptathio-phenyl derivative that shows potent antianaphylactic and antihistaminic activity in animals. Ketotifen also inhibits chemically induced release of histamine from rat peritoneal mast cells by compound 48/80 in vitro.² Oral ketotifen has shown a protective effect against allergen-induced bronchoconstriction in adults with atopic asthma³ but not in children.⁴ We report a longer-term comparison of ketotifen and placebo in adult asthma.

Patients and methods

We recruited 50 patients (34 men and 16 women) aged 16-66 years (mean age 36 years) from 12 centres. All had a forced expiratory volume in one second (FEV₁) above 40% of their predicted value, reacted to skin-prick tests with common allergens, and showed a greater than 20% improvement in FEV₁ after inhaling a bronchodilator. Patients taking tablets of corticosteroid were excluded, but those who inhaled a constant dosage of corticosteroid were included. Patients in whom the potential effect of drowsiness might have proved dangerous were not eligible. Sodium cromoglycate was not permitted during the four weeks before entry. Bronchodilators other than inhaled salbutamol for symptomatic relief were stopped.