lower than those currently believed to have adverse effects on health. Thus it seems unlikely that this pollutant would have caused our findings.

Possibly the combustion products of coal gas and natural gas differ in some relevant way. We could not separate the effects of the two types of gas because most of the study areas underwent a changeover from town to natural gas during 1973, and the children were exposed to the products of combustion of both gases.

The relation between gas cooking and respiratory disease seems to be stronger and more consistent for girls than for boys, as would be expected if girls spent more time in the family kitchen. If this is the case, and the difference between the sexes is purely the result of differing exposure, it seems likely that increased ventilation might be sufficient to dispel any risk.

Nevertheless, detailed research is required to determine whether the relation we have found is really due to a direct effect of the products of gas combustion on the respiratory tract before more complicated measures for the protection of health are considered.

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Dextrostix-Eyetone in the insulin hypoglycaemia test

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Summary

The Ames Dextrostix-Eyetone system was evaluated for monitoring the blood glucose concentration during insulin-induced hypoglycaemia. The results agreed well with laboratory values for plasma glucose, obtained by an orthotoluidine method, and the method was practicable as a bedside technique. In two cases quick results obtained with the Eyetone enabled the insulin tolerance test to be interrupted to prevent severe hypoglycaemia before the clinical indications were obvious. The extra time and effort required were minimal, and its value

seems to far outweigh the disadvantage of the extra work entailed. Nevertheless, care in using the system was important, and the operator must familiarise himself with the system before the most reliable results can be obtained.

Introduction

The best validated test of pituitary growth hormone (GH) release in man is the insulin tolerance test (ITT), which allows GH and ACTH production by the pituitary to be assessed simultaneously.¹ The test is especially useful as thyrotrophin-releasing hormone (TRH) and gonadotrophin-releasing hormone (GRH) may be given at the same time so that prolactin and gonadotrophin secretion can be assessed simultaneously.

Adequate hypoglycaemia must be achieved before the ITT can be considered to be satisfactorily completed. Hypoglycaemia is generally recognised from the clinical signs (such as sweating) and, retrospectively, by seeing that the plasma glucose concentration has fallen by at least 50% from the fasting value and is below 2.8 mmol/l (50 mg/100 ml) at the nadir.² Because of this and of the danger of severe hypoglycaemia, especially in young children, there have been extensive searches for other

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methods of stimulating pituitary function. The most popular alternatives have been arginine infusion, glucagon, Bovril, and exercise, but none of these are convincingly reliable.

Much, if not all, of the danger of the ITT would be obviated if the fall in blood glucose concentration could be accurately monitored at the bedside. This would allow the doctor to administer intravenous glucose before severe symptoms become manifest. Normally it is unreasonable to expect a routine laboratory to assay multiple blood samples immediately, and the use of Dextrostix reagent strips (Ames Company Division, Miles Laboratories, Slough), read by eye, is only semi-quantitative, especially in the range of blood glucose below 2.8 mmol/l (50 mg/100 ml).

In 1970 an electronic instrument for reading Dextrostix reagent strips was introduced by Ames. This has proved useful in studies of diabetes and induced hypoglycaemia,^{3,4} although slightly poorer correlations at the extremes of glucose concentration have also been reported.^{5,6} More recently Eyetone, a more advanced version of the reflectance meter, has been introduced by the same company. Unlike the former instrument, it uses a two-point calibration at glucose concentrations of 2.8 and 22.2 mmol/l (50 and 400 mg/100 ml) in whole blood, is mains-operated, and has more sophisticated electronics. In 1974 a three-centre study of the instrument⁷ reported that it was a significant improvement on the original reflectance meter and a quick and reliable alternative to conventional laboratory methods.

We thus conducted a trial of the Eyetone reflectance meter during routine ITTs on children being investigated for short stature. This allowed a detailed study of the instrument at low glucose concentrations, and an assessment of its usefulness in this particular clinical condition.

Patients and methods

Twenty-three patients aged 4.2 to 16.8 years were studied; all were being investigated for short stature. Hypopituitarism was the final diagnosis in 15 of the patients: one had associated thyrotrophin deficiency, and the remainder apparently had "isolated" GH deficiency. The rest were ultimately determined to have normal pituitary function.

All the ITTs and Dextrostix-Eyetone measurements were performed by one clinician (MAP). During each test a butterfly needle (Abbott Laboratories) was inserted into an antecubital vein and retained there throughout the study. After an initial blood sample had been taken 0.1 IU/kg body weight of soluble insulin (Wellcome) was injected through the same needle. In 14 cases this was given together with 200 µg of TRH and 100 µg of GRH.

Blood samples were withdrawn at 0, 15, 30, 45, and 60 minutes and in some cases at 90 minutes. A drop of each blood sample was used for measuring blood glucose by the Dextrostix-Eyetone method, and the remainder was aliquoted for the various hormone assays. The Eyetone estimations were performed immediately. If clinically indicated, or if the previous blood glucose concentration was suspiciously low, intermediate samples for blood glucose were taken as necessary. Whenever blood glucose was estimated by the Dextrostix-Eyetone method a sample was also placed in a fluoride-containing sample tube for subsequent laboratory assay. A total of 133 samples were studied.

Dextrostix-Eyetone assay of blood glucose levels—The details of the chemical reactions have been described.⁸ A drop of blood, large enough to cover the reagent area, was placed on the Dextrostix strip. After exactly 60 seconds the excess blood was washed off rapidly using a wash bottle and the strip blotted dry. The strip was then inserted into the Eyetone instrument, previously calibrated, and the blood glucose concentration read. The whole procedure took one and a half to two minutes. Before using the Dextrostix reagent strips care was always taken to ensure that they were suitable for use, by comparing the colour of the reagent area with the zero block of the colour chart on the bottle, as recommended by the manufacturer. If the strips were darker than the zero colour block the whole bottle of Dextrostix was discarded.

Laboratory measurements of plasma glucose—All samples for plasma glucose estimations were collected into sample tubes containing fluoride. They were all assayed in the department of chemical path-

ology, Hospital for Sick Children, Great Ormond Street, by the orthotoluidine method of Cooper and McDaniel.⁹ As Schersten *et al*⁷ have shown that the packed cell volume has no significant effect on Dextrostix and as all patients in the study had normal haemoglobin concentrations, we made no allowance for the packed cell volume. Nevertheless, the laboratory method measured plasma glucose, not whole blood glucose, so that a small systematic difference between the Dextrostix-Eyetone values and laboratory values should be expected.

The whole study took seven months, during which time the same Eyetone instrument and the same laboratory techniques were used.

Results

The correlation between Dextrostix-Eyetone and laboratory glucose values in all 133 samples is shown in the figure. The correlation coefficient was 0.96 and the regression equation was: laboratory (mmol/l) = 0.19 + 0.96 Dextrostix-Eyetone (mmol/l). The standard error for the regression coefficient was 0.02 and that for the intercept was 0.07. The regression coefficient was highly significantly different from zero ($P < 0.001$), though not from 1.0, whereas the intercept was significantly different from zero ($P < 0.05$). The standard error of estimate of a single laboratory value from a single Eyetone value was 0.32 mmol/l (5.7 mg/100 ml) at values around the mean and, at the extremes, 0.33 mmol/l (5.9 mg/100 ml).

Laboratory and Dextrostix-Eyetone values for plasma and blood glucose respectively. At the five points marked ▲ two pairs of values exactly coincide; at the two points marked ▽ three pairs coincide.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

The table shows the values of the correlation coefficients between laboratory and Dextrostix-Eyetone estimates at each sampling time. There were 23 readings at each time except at 90 minutes, when only 13 blood samples were taken. The remaining five samples were taken at intermediate times. There was no trend in the degree of correlation, although the correlation at 60 minutes (0.89) was significantly lower ($P < 0.05$) than that at 15 minutes (0.97), which was the highest obtained. The 60-minute group included the sample in which the greatest discordance was found (see below). The degree of correlation was independent of the mean glucose concentration.

The importance of familiarity with the instrument was also tested. Comparing the first 69 samples with the second 64 (a purely arbitrary division between the 12th and the 13th patients) the residual variance fell from 59.7 to 19.8 (mmol/l)², which is highly significant ($P < 0.001$).

No "acclimatisation" period was allowed for before the start of the study, so that this particular aspect could be investigated.

Two investigations were interrupted by intravenous injections of 25% glucose. On both occasions this was because of very low values of blood glucose as determined by the Dextrostix-Eyetone system on the 15-minute sample (0.60 and 0.67 mmol/l (11 and 12 mg/100 ml)) followed five minutes later by a lower or substantially unchanged value (0.56 and 0.78 mmol/l (10 and 14 mg/100 ml)). In both cases the patients were showing clinical signs of hypoglycaemia, but, without the Dextrostix-Eyetone results these would not have been enough to have caused the investigator to terminate the study. The laboratory values for these same four samples agreed well with the Dextrostix-Eyetone values. No other patient showed hypoglycaemic symptoms severe enough to terminate the investigation without such very low Dextrostix-Eyetone values. Equally, there were no very low values returned from the laboratory after the investigation where higher, spuriously reassuring, values had been found at the bedside.

The greatest discordance for a single value was seen when the Dextrostix-Eyetone system suggested a value of 2.8 mmol/l (50 mg/100 ml) and the laboratory value was only 1.28 (23 mg/100 ml). There was no obvious reason for this discrepancy, and this extreme difference may have been due to an unknown external factor. This point lay more than six standard deviations from the regression line, when this was calculated after excluding the outlier, and it certainly seems not to reflect the usual relation between laboratory and Dextrostix-Eyetone values. It has, however, been included in all calculations, except as noted in the table.

Mean glucose values and correlation coefficients for Dextrostix-Eyetone and laboratory determinations at each sampling time.

Time (min)	Mean (SE of mean) glucose concentration (mmol/l)		Correlation coefficient
	Eyetone system	Laboratory	
0	4.13 : 0.21	4.22 : 0.19	0.97
15	2.04 : 0.24	2.15 : 0.24	0.97
30	1.93 : 0.17	1.93 : 0.16	0.95
45	2.36 : 0.19	2.47 : 0.18	0.94
60	3.04 : 0.21	2.96 : 0.20	0.89 (0.94)*
90	3.21 : 0.24	3.22 : 0.24	0.93

*Value in parentheses is for group of samples with extreme outlier excluded (see text).
Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

Finally, deteriorated Dextrostix were used intentionally in one patient who was excluded from the numerical analysis. The deterioration was judged by the colour of the reagent area of the strip being substantially darker than the zero point of the bottle colour chart. The results were extremely discordant, with a bias towards overestimating the blood glucose concentration. This confirms the need for assessing the condition of the Dextrostix before use, as indicated in the manufacturer's instructions.

Discussion

When blood sampling is being performed at 15-minute intervals or longer, the one and a half to two minutes needed to perform the Dextrostix-Eyetone measurements is easily absorbed. On several occasions it was perfectly possible to perform ITTs on two patients simultaneously. It is, however, better to have the instrument actually at the bedside, rather than in a side room, so that the patient need never be left. In most paediatric wards it is not convenient to keep the instrument in this way, so the Eyetone will probably be switched on and off between investigations. It is therefore important that the machine is given at least 30 minutes to stabilise after first being switched on. Preferably the instrument should be left on continuously, as this does not shorten its working life and achieves maximum stability.

There was a consistent difference between the plasma glucose values and the whole-blood glucose values, with a positive intercept of 0.19 mmol/l (3.4 mg/100 ml). This indicates that the plasma values from the laboratory were consistently slightly higher than the whole-blood values, as expected. Apart from this, and in common with other recent studies,^{3-8 10 11} the

Dextrostix-Eyetone and laboratory measurements agreed well. Only one sample gave misleading results, and this was not in a critical region of blood glucose values. We have considered lower blood glucose concentrations in more detail than other workers, and our findings have also shown that the Dextrostix-Eyetone method is practical for bedside use and provides a reliable guide to events.

In two cases an ITT which might otherwise have resulted in prolonged, severe hypoglycaemia was interrupted, and correctly so, as judged by the subsequent laboratory-determined plasma glucose concentrations. In these two cases hypoglycaemia was reversed before the patient showed severe symptoms; this must have reduced substantially any risk to the patient. It has long been recommended, when performing an ITT, that if the patient is thought to be ACTH deficient as well as GH deficient, a smaller dose of insulin should be given (usually 0.05 IU/kg). This is sound advice, but in our study there was no reason to believe that either of the two patients who became severely hypoglycaemic were in this category, and all our patients were given a dose of 0.1 IU/kg. Indeed, the result of the test in both cases showed normal cortisol production, although both patients had isolated GH deficiency. They would therefore have normally been given the full dose of insulin, as indeed they were. The Dextrostix-Eyetone system therefore provided extra safety for these children.

The method also helped in a complementary manner. General experience with the ITT has shown that some patients fail to achieve adequate hypoglycaemia (probably when they have normal pituitary function), and the result is therefore equivocal. One such case occurred in this study; a second dose of insulin (0.05 IU/kg) was given at 30 minutes and the blood glucose concentration (Dextrostix-Eyetone) subsequently fell to 1.22 mmol/l (22 mg/100 ml) (the laboratory value was 1.44 mmol/l (26 mg/100 ml)). A normal growth hormone response was seen. This would probably not have occurred without the second dose of insulin, at which time the blood glucose concentration was 3.05 mmol/l by the Dextrostix-Eyetone method and 2.83 mmol/l by the laboratory method (55 and 51 mg/100 ml respectively). This patient was thus saved the inconvenience of a repeat investigation at a later date.

In conclusion, we think that the Dextrostix-Eyetone system has a useful part to play in the performance of ITTs both by assuring the safety of the patient and by ensuring that a valid investigation is completed. We would, however, emphasise that the user must be experienced in using the system before maximum precision is obtained.

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