Laboratory assessment of three reflectance meters designed for self monitoring of blood glucose concentrations

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SUMMARY Three monitors designed for self monitoring of blood glucose concentrations by diabetic patients were evaluated in a laboratory. All three assessments correlated positively with a laboratory reference method based on glucose oxidase. Coefficients of variation at all levels tested were less than 10% for each monitor. Stability of the colour development of each stick was assessed and the effects of changes in blood spot volume and incubation time were examined. Twelve ward nurses were each asked to measure two blood samples and the results obtained showed wide variability. Overall, our findings suggest that each of the three monitors tested is suitable for use in monitoring capillary blood glucose concentrations by those who are properly trained.

Self monitoring of blood glucose concentrations (SMBG) is common in the routine management of diabetic patients. Quantitative measurement of glucose concentration in capillary blood by the patient has been made possible by the introduction of reflectance meters which read the degree of colour change in glucose oxidase based reagent strips.¹ Such measurements facilitate a major goal of diabetic management—that is, the maintenance of blood glucose values as close as possible to those of non-diabetic subjects without hypoglycaemia.^{2,3} Measurements of urinary glucose concentrations are less satisfactory; they correlate poorly with the prevailing blood glucose concentration,^{4,5} depend on the renal threshold which varies both between and within subjects,⁶ and give no information on blood glucose concentrations below the renal threshold, and therefore cannot detect hypoglycaemia.⁷

The American Diabetes Association³ identified groups of patients in whom SMBG is strongly recommended—namely; (i) those receiving intensive insulin treatment; (ii) those who are pregnant or who are planning pregnancy; (iii) patients prone to hypoglycaemic attacks.

The Association encouraged the use of SMBG for the routine management of diabetics requiring insulin.

The commercial implications of SMBG are evident in the number of new and improved instruments produced. We assessed the performance of three such

instruments—two current market leaders (Reflolux II, Glucometer II) and a monitor new to the British market, Glucospot, which is currently available in the United States of America and Europe as Glucoscot II. Our assessment consisted of a comparison of monitor results with a laboratory method, examination of potential sources of error, and a small trial of each instrument's performance in the hands of ward nurses.

Material and methods

INSTRUMENTS

Glucometer II (Ames Division, Miles Laboratories, UK). This is a development of the Glucometer and differs from its predecessor in having predetermined calibration codes, in using the faster reacting Glucostix, and in using a blot dry technique, which replaces the water wash used previously. Controls consist of three buttons—an on/off button, a programme button to select a calibration programme appropriate for the batch of reagent strips used, and a start button which activates the timing cycle. This consists of a lag phase of eight seconds to allow time for a blood spot to form after capillary puncture. An audible signal announces the beginning of the incubation cycle when blood should be applied to the strip and a second warning signal indicates the end of the cycle when the strip is blotted dry. The strip is then placed in the test chamber where it is automatically read. A liquid crystal display shows results in mmol/l. The analytical range quoted is 2.2–22.2 mmol/l, with values outside this range being indicated by “Lo” and “Hi”, respectively.

Reflolux II (*Boehringer Mannheim/BCL, Lewes, UK*) This instrument is a development of Reflolux, differing from its predecessor in that it has a wider analytical range (0.5–27.7 mmol/l), no requirement for blank reading of reagent strips, and a memory in which lot specific, bar-coded information can be stored. The previous system required calibration data to be loaded before each period of analysis. The timing cycle consists of a 60 second incubation period, following which blood is wiped from the strip and colour is allowed to develop for a further 60 seconds. Results are displayed in mmol/l with results above or below the analytical range indicated by HHH or “LLL”, respectively.

Glucospot (*Clandon Scientific Ltd, Aldershot, UK*)

This instrument is a new meter proposed for the British market and currently available in the United States of America and Europe as Glucoscot II (Kyoto Daiichi Kagaku Co, Ltd, Kyoto, Japan). Glucostrip reagent strips are read with an analytical range of 0.6–33.3 mmol/l. The reaction cycle is two minutes, a 60 second incubation period following which blood is wiped from the strip, and a further 60 seconds of colour development. A large liquid crystal display gives results in mmol/l. Results beyond the analytical range are indicated by Hi or Lo warnings. Predetermined, lot specific calibration codes are incorporated into the instrument's memory, the appropriate code being selected before use.

The reaction principle of all strips is based on the glucose oxidase/peroxidase system, and strips may be read visually in addition to use of the meter. Instruments are compact and readily transportable, and comprehensive instructions are given on their use in all cases.

METHODS OF ASSESSMENT

Accuracy was determined for each meter by comparison of results with those of a laboratory glucose oxidase method (YSI 23AM, Clandon Instruments, UK Ltd), the accuracy of which was known from performance in external quality control schemes. One hundred heparinised samples covering the analytical ranges of each of the instruments, were assayed in duplicate by meter and simultaneously by the laboratory method. Results were compared by regression analysis using Deming's method.⁸ Assay coefficient of variation (CV) was assessed by paired replicate analysis of results obtained, CVs being calculated for all results and each of three subgroups of results—0–4, 4–10, and > 10 mmol/l. Intrabatch precision was also assessed by replicate ($\times 20$) analysis of two blood samples.

To assess the effect of changes in blood spot volume repeated measurements of a single blood sample (YSI value = 8.2 mmol/l) were performed for a range of

blood spot volumes between 10 and 100 μ l, applied to the strip using an adjustable positive displacement micro pipette.

The effect of changes in blood contact time was assessed for each instrument by allowing contact for the recommended time for each instrument ($T \pm 2, 5, 10$ and 15 seconds and otherwise following instructions. Regression analysis was used to determine the significance of observed changes.

Stability of developed colour was determined by assaying blood glucose at two levels and taking regular readings of the developed colour for up to two hours. Both Reflolux and Glucospot have a stat read facility which allowed frequent readings to be taken over the first three minutes. The Glucometer has no such facility, and readings at one minute intervals only were possible. We used the Triggs method of trend analysis⁹ to determine the significance of changes in glucose concentration.

Finally, a short trial of the instruments' performance when used by ward nursing staff, was carried out. Twelve trained nurses were given individual verbal instruction in the use of each instrument and were asked to perform one-off measurements of two blood heparinised samples. The samples were cooled in iced water to minimise reduction in glucose concentration¹⁰ and each was assayed five times by the YSI method at the beginning and end of the test period. Samples were thoroughly mixed before assay and instruments were used in a random order by the nurses.

Apart from the analyses carried out by the nursing staff, all analyses were performed by one of us (JB), who has several years experience of bench work in a clinical laboratory.

Results

ACCURACY

Figs 1a–c are scattergrams showing the correlation between each of the monitors and the laboratory reference method. Table 1 shows the correlation coefficients derived from these data, together with the regression equations, as calculated by Deming's method, where the regression equation is: monitor result = regression coefficient $\times$ YSI result.

Table 1 Values for regression equation and correlation coefficient (r) for each monitor

Monitor	Regression equation	r
Glucometer II	0.90 (YSI) + 0.17	0.95
Reflolux II	0.88 (YSI) + 0.19	0.98
Glucospot	0.83 (YSI) + 0.17	0.96

Fig 1 Correlation between laboratory method and (a) Glucometer II results; (b) Reflolux II results; (c) Glucospot results.

PRECISION

Table 2 shows assay CVs based on paired replicate analysis of all results and each of the three subgroups

Table 2 Assay CVs for all results and each of three subsets of results

	Glucometer II	Reflolux II	Glucospot
<i>All results:</i>			
Mean (SD)	6.91 (0.44)	7.38 (0.31)	8.79 (0.78)
CV (%)	6.32	4.22	8.85
<i>0-4 mmol/l:</i>			
Mean (SD)	3.12 (0.19)	2.91 (0.14)	2.64 (0.24)
CV (%)	5.94	4.81	9.00
<i>4-10 mmol/l:</i>			
Mean (SD)	5.82 (0.24)	6.42 (0.21)	6.50 (0.25)
CV (%)	4.10	3.26	3.81
<i>> 10 mmol/l:</i>			
Mean (SD)	12.72 (0.73)	13.81 (0.52)	17.72 (1.30)
CV (%)	5.79	3.80	7.53

of results defined. The mean and standard deviation (SD) for each group of results are also included. To assess intrabatch precision two blood samples with blood glucose concentrations of 2.3 mmol/l and 12.0 mmol/l, as measured by the YSI method, were each assayed 20 times by each monitor. Table 3 shows the CVs for each monitor.

Table 3 Percentage intrabatch precision based on repeated assay ($n = 20$) of two blood samples

	Sample 1 (YSI value = 2.3 mmol/l)	Sample 2 (YSI value = 12.0 mmol/l)
Glucometer II	3.2	7.0
Reflolux II	5.5	4.6
Glucospot	4.7	5.0

Fig 2 Stability of developed colour, measured by change in blood glucose concentration over two hours.

Fig 3 Effect of blood contact time on glucose concentration. (T represents recommended contact time for each monitor).

Fig 4 Effect of blood spot volume on glucose concentration.

STABILITY OF DEVELOPED COLOUR

Fig 2 shows the trends observed for each monitor, when readings were taken at intervals after completion of the normal cycle. Trend analysis indicated significant changes as follows:

- (i) *High value*: after 30 minutes for Glucometer, between four minutes and 60 minutes for Reflolux, and between two minutes and 60 minutes for Glucospot.
- (ii) *Low value*: after five minutes for Glucometer, after seven minutes for Reflolux, and after three minutes for Glucospot.

EFFECT OF BLOOD CONTACT TIME

Fig 3 shows the variation in blood glucose concentration obtained with a change in blood contact time, above and below that recommended. From the regression equation for each meter, where glucose concentration = slope $\times$ contact time + intercept, slopes were obtained of 0.21 for Glucometer, 0.06 for Reflolux, and 0.07 for Glucospot. This suggests that a small deviation from the recommended contact time will result in greater error in the estimate of glucose concentration with Glucometer, presumably reflecting the faster reaction time of Glucostix strips.

EFFECT OF BLOOD SPOT VOLUME

Fig 4 shows the variation in blood glucose concentration obtained with variation in volume of blood spot applied to each of the strips. It is evident that blood spot volumes less than 30 μ l affect results from Glucometer and Glucospot while Reflolux results are unaffected over the range tested.

RESULTS OBTAINED BY NURSES

Over the period of testing (two hours) there was a 10% reduction in glucose concentration in both samples (YSI values - 17.4-15.6, 4.4-3.9, each figure being the mean of five measurements) (fig 5). While accepting that this trend would be expected to increase the range of values obtained, the results presented were randomly scattered over the test period, showing no trend with time. In addition, any such error introduced should equally affect all three monitors. We believe,

Fig 5 Scatter of results obtained for two blood samples by 12 ward nurses.

therefore, that these results are a reflection of variability between operators.

Discussion

Each of the three monitors tested was compact, easy to use, and had clear instructions supplied by the manufacturer. Though correct technique is thus encouraged, potential sources of error have been identified^{7,11} including volume of blood spot, length of time during which blood is in contact with the strip, and the time of reading after colour development. We found lower readings with volumes less than 30 μ l for both Glucometer and Glucospot while little change was seen in values obtained with Reflolux over the range of volumes tested. In varying blood contact time, the greatest change was observed with the faster reacting Glucostix. Our figures for colour stability

show that significant changes in colour development continue to occur after completion of the cycle, and are most pronounced at higher glucose concentrations. The clinical importance of this finding, however, is open to question.

Just how accurate monitors should be remains unresolved. Desirable analytical goals for laboratory measurement of glucose have been summarised by Fraser.¹² It would be unrealistic to expect such levels of performance from untrained staff. Fraser also reviewed a number of studies in which the views of clinicians on desirable levels of precision for glucose analysis were sought. Great variation between studies was found, possibly attributable to the question asked. Tonks¹³ related the acceptable error of analysis to biological variation by the formula:

$$\text{Acceptable limits of error (\%)} = \frac{\frac{1}{2}(\text{normal range})}{\text{mean of normal range}} = 100\%$$

with the stipulation that where calculated error exceeded 10%, as in the case of glucose, a maximum of 10% should apply. Performance in the hands of trained laboratory personnel is, however, no guide to performance outside the laboratory. Examination of results from sources outside the laboratory has shown a poor standard of performance when compared with laboratory results,^{14,15} and the variation in results obtained by ward nurses in our small study seems to confirm this finding.

In routine use doubts have emerged as to the reliability of reporting by patients.¹⁶ Despite reservations, however, a consensus view suggests that blood glucose monitors are sufficiently accurate for routine use,⁶ and when used by properly trained staff with attention paid to technique, are accurate to within 10%.^{16,17} If this level of performance is acceptable the results of our assessment suggest that in the hands of an adequately trained and motivated person, each of the three monitors tested can consistently produce results suitable for clinical use in the therapeutic monitoring of diabetes mellitus.

Our data do suggest, however, that Reflolux is the most reliable of the three instruments, both when handled by nursing staff and experienced laboratory workers. This is a reflection of the relative insensitivity of Reflolux to small changes in blood volume and contact time compared with the other two instruments. Others have also found that Reflolux is a more reliable instrument than the Glucometer.¹⁸

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