Comparison of two reflectance photometers in the assessment of neonatal hypoglycaemia

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Abstract
To assess the accuracy and reliability of reflectance photometers in estimating blood glucose concentrations, two were assessed: the Ames Glucometer 3 (Bayer Diagnostics) with Glucofilm Test strips; and the Reflox S (Boehringer Mannheim) with BM Test Glycemia 20-800 strips. These were compared with laboratory blood glucose estimations in 100 assays (50 comparisons for each machine, measuring the difference (d) between the glucose reading and the mean of the reflectance photometer and the laboratory value). The Ames Glucometer 3 (mean d=+0.7 mmol/l, (SD 1.1) mmol/l) was less accurate than the Boehringer Refflux S (mean d=0.2 mmol/l, (SD 0.7) mmol/l).

The range of error of both machines is wide (Ames 2 SD range +2.9 mmol/l to $-1.5$ mmol/l true readings; Boehringer +1.8 mmol/l to $-1.2$ mmol/l of true readings). Because of this, any reflectance photometer readings that are even slightly low should be checked with laboratory estimations. The clinical value of such machines is limited in infants with low blood glucose concentrations.

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Hypoglycaemia in newborns is a subject of some controversy concerning safe concentrations of blood glucose and the attendant neurological risk to babies. A reliable method for measuring blood glucose in newborn infants is therefore needed. Reflectance photometers are widely used in neonatal intensive care to measure blood glucose concentrations, because they are less expensive than laboratory analysis, can be performed at the bedside, and require only small volumes of blood.

This study compares the accuracy of two reflectance photometers in daily use in a neonatal intensive care unit with standard laboratory analysis (Kodak Ektachem 250 analyser).

Methods
The two reflectance photometers used were: (A) the Refflux S (Boehringer Mannheim) BM Test Glycemia 20-800 strips, glucose-oxidase/peroxidase reaction (diagnostic range 0.5–27.0 mmol/l); (B) the Ames Glucometer 3 (Bayer Diagnostics) Glucofilm Test strips, glucose oxidase method (diagnostic range 1.1–27.7 mmol/l).

Specimens were also analysed using the Kodak Ektachem 250 colorimetry analyser with dry chemistry slide technology. The dynamic range of this analyser is 1.1–34.7. The Ektachem 250 analyser was calibrated according to the manufacturer’s requirements. The analyser’s performance on standard quality controls for normal blood glucose is mean 5.1 mmol/l (SD 0.2) mmol/l. Quality control results for high range are: mean 13.4 mmol/l, (SD 0.3) mmol/l; controls for the lower range values are not specifically required by the manufacturer’s guidelines. The clinical accuracy of the Kodak Ektachem 250 is regularly monitored in compliance with the quality control standards of Murex Diagnostics international clinical chemistry programme.

Blood samples were taken from 30 babies being managed in the special care nursery, mean age 12.5 days, gestations between 23.4–41.2 weeks, and with a median birth-weight of 958 g. One hundred samples were assayed, 50 using machine A and 50 using machine B. Samples were collected sequentially. The two reflectance photometers were calibrated before use and a new bottle of reagent strips was used for each machine.

Samples were collected from indwelling arterial lines or by capillary sampling. Venous blood was not used. As a result of concerns about errors in blood estimations of glucose in specimens with either a high or low haematocrit, haemoglobin and packed cell volume (PCV) were measured with all specimens. Specimens of haemoglobin and PCV were collected in EDTA tubes and specimens for plasma glucose assays were collected in heparin lithium tubes. Laboratory and clinical blood glucose samples were collected simultaneously.

All assays were stored at room temperature and processed within 30 minutes of collection, most reaching the laboratory within 10 minutes. Close attention was paid to this detail to minimise the effect of glycolysis – estimated to occur at a rate of up to 7% per hour. Test strip analyses were performed in the ward minutes after each blood sample was taken.

All nursing staff in the neonatal unit were trained in the use of these machines. There was no specially selected group of operators. Each operator was required to perform a control assessment of their technique before each assay. All samples were collected simultaneously, after the operator controls had been performed.

STATISTICAL METHODS
Agreement between the reflectance meter reading and the laboratory assay of blood glucose
was analysed using the method of Bland and Altman. This method examines the correlation of the difference between the two measurements with the mean of the values derived by the two methods under comparison. Using this technique, the difference has a value of zero if the two methods agree and the error is likely to be normally distributed. The mean is used, because both measurements are estimates of an unknown true value and the mean is taken as the best available estimate of this value.

The study protocol was approved by the Research and Ethics Committee of the Mercy Hospital for Women. Specific consent to participate in this study was not sought from parents as the study was performed as a unit 'quality control' exercise, using blood specimens which would normally have been taken in the routine clinical management of these infants. No additional specimens were taken for the purposes of this study.

**Results**

The results of measurements using each machine are shown in figs 1 and 2. The Boehringer Reflolux S had a mean (d) = 0.2 (SD 0.7) mmol/l. The Ames Glucometer 3 showed a greater variation with a mean (d) = 0.7 (SD 1.1) mmol/l.

Comparable inaccuracies at both high and low readings were noted with both reflectance photometers. Only a relatively small number of high glucose concentrations, however, were seen, most results being in the low to normal range.

All operator control calibrations were within the limits specified by the manufacturers (Ames Glucometer 3 manufacturer’s range 4.7–7.2 mmol/l, operator’s 5.6–6.5 mmol/l. Boehringer Reflolux S range 1.9–3.6 mmol/l, operator’s controls 2.2–2.8 mmol/l). Operator techniques were therefore satisfactory.

All specimens analysed using the Ames Glucometer 3 had a PCV within the manufacturer’s recommended range (20–60%). The manufacturer’s recommended range of PCV for the Boehringer Reflolux S was 35–55%. In this group 90% of specimens had a PCV between 35–55%, 2% had a PCV of >55%, and 8% were between 33–35% Figs 3 and 4 plot the mean (d) value against the respective PCV for each photometer.

We observed that 82% of whole blood estimations performed using the Ames Glucometer 3 estimated the glucose to be higher than the anticipated plasma glucose value. This is not the expected relation, plasma estimations generally giving a higher result than whole blood. There was no consistent difference between whole blood estimations performed using the Boehringer Reflolux S and laboratory plasma glucose measurements; 56% of whole blood estimations were higher than plasma glucose.

Of the specimens analysed with the Ames Glucometer 3, 62% were capillary samples and 38% arterial assays taken from indwelling arterial lines. Fifty two per cent of specimens analysed with the Boehringer Reflolux S were capillary and 48% arterial. The standard deviations (d values) of whole blood estimations
were almost identical between the two groups using both methods of collection, (Ames Glucometer 3 capillary specimen SD 0-52, arterial SD 0-54; Boehringer Reflux S capillary SD 0-84, arterial SD 0-84). This suggests that there were no significant differences in operator or sampling error between the two sampling methods.

Discussion
When using reflectance photometers, it is important to consider whether they are being used as a screening device or as a definitive assay. If these machines cannot be shown to produce accurate and reproducible results then their value is very limited and more accurate methods must be used to guide treatment. Even a screening device should be clinically accurate.

In this study the Boehringer Reflux S was more accurate than the Ames Glucometer 3, but even the SD of 0-7 mmol/l for the Boehringer Reflux S remains a concern when measuring the low concentrations of blood glucose in newborn infants.

The clinical implication of the relatively large standard deviation of both techniques is that two consecutive blood glucose results may indicate that a hypoglycaemic state has 'naturally' corrected itself, when there has been no true change in the biochemistry and that clinically important hypoglycaemia may go undetected. This error is unpredictable for both test strip methods, especially when interpreting a reading from a single baby in the clinical setting.

When comparing one photometer with another, the results from the two machines could not be assumed to have equal meaning. There was also no consistent bias in any of the results and therefore no correction factor could be applied to any readings so generated.

Reflectance photometers are subject to multiple factors that can significantly alter their reliability. In recent years there has been much emphasis on the importance of ruling out operator error. It is acknowledged that this is a large variable, but it seems that other factors may be of equal importance. In our study the operator controls were within the stipulated range. These controls indicate that errors of timing, wiping, droplet size and stick insertion have been eliminated, along with errors related to machine calibration. The manufacturer's allowance of a 1-7-2-4 mmol/l variation in the quality controls is in itself an acknowledgement of the wide range of error in whole blood measures using reflectance photometry. It has been suggested that allowance needs to be made for the 10%-15% variation in plasma over whole blood estimations, plasma glucose values being said to be higher.9 Our results showed whole blood concentrations were higher than plasma particularly when measured using the Ames Glucometer 3. We cannot explain this.

Haematocrit values of <35% may yield results up to 10% higher and values of >55% may give results that are 15% lower.10 Hypoglycaemia may then be missed in anaemic infants and perhaps overdiagnosed in polycythaemic infants. Nearly all specimens were within the normal range and therefore this cannot account for the observed effect. We were unable to determine the factors responsible for any errors in the small group of infants with PCVs below the recommended range for reflectance photometers.

Venous samples were not used in this study as they yield an estimated result 15% lower than arterial blood and because venous sampling is not routinely used in newborn infants in our nursery because of the technical difficulty involved.10 Arterial and capillary samples were compared as a means of assessing technique. Capillary samples can yield lower values as a result of decreased peripheral perfusion, excessive squeezing, and contamination by the skin preparation agent before collection.6 The data showed no difference between the accuracy of capillary and arterial collection methods.

In conclusion, blood glucose results obtained using whole blood estimations of reflectance photometers must be interpreted with caution. Nurseries introducing such techniques or changing to a different machine should perform careful quality control studies to ensure that the system chosen produces clinically useful and reliable results. No assumptions should be made about comparability between measurements generated by different systems until such studies have been performed.

Even as a screening tool, the clinical value of these reflectance photometers is limited by relatively large and unpredictable errors. For example, to be 95% certain that an infant is not hypoglycaemic, using 2-0 mmol/l as the threshold, a reflectance photometer reading of 3-4 mmol/l would be needed, using the Boehringer Reflux S, the least inaccurate of the two machines. Few neonatal units apply so rigorous a standard.

As the blood glucose concentration at which significant neurologic changes occur is so uncertain1 2 it would seem sensible to either avoid the use of reflectance photometers altogether for infants at risk of hypoglycaemia or to treat estimations so obtained with real suspicion unless confirmed by laboratory estimations.

An alternative method of blood glucose monitoring is still required. At the present time colorimetry autoanalysers remain the 'gold standard'. Satellite laboratories within the special care nurseries may provide the clinician with accessible accurate results. Experience with the bench top Yellow Springs Instrument Company glucose analyser (YSI 23A) has shown comparable results with a precise technique, but laboratory estimations were still recommended for abnormal assays.11 12 The YSI uses a glucose oxidase membrane applied to a hydrogen peroxide sensor to ascertain the glucose concentration of whole blood in 45 seconds.13

These satellite laboratories are an alternative method superior to reagent strip analysis, but
their accuracy in relation to autoanalysers such as the Kodak Ektachem 250 will need to be verified by further research.

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