

Glucose and lactate in neonatology (clinical focus)

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Both high and low blood glucose levels may be dangerous to the newborn baby. Measurement of blood or plasma lactate concentrations gives an indication of the adequacy of oxygen delivery to tissues, and blood and CSF lactate levels are essential investigations in the diagnosis of inborn errors of metabolism (IEM).

The requirement for frequent tests and rapid results suggests that near-patient testing is the ideal. However, most near-patient testing devices do not have the sufficient accuracy required given the limited range of optimal blood glucose and lactate values. Neonatal unit laboratory instruments now appear to hold the solution.

The clinical significance of circulating glucose and lactate concentrations

Glucose

It has been recognized for many years that both high and low blood glucose levels may be dangerous to

the newborn baby [1]. Therefore, in at-risk groups (see below) it is essential to have accurate and regular monitoring of blood glucose concentrations so that prolonged periods of disordered blood glucose homeostasis may be prevented.

However, one cannot define single cut-off values above or below which damage may occur and, as with all aspects of neonatology, our aim is to treat the baby's clinical condition and not a number (the blood glucose concentration).

At-risk groups:

- Moderately preterm or growth-retarded babies - blood glucose monitoring is an adjunct to the support and optimization of breast feeding and along with clinical assessment may indicate when formula supplements are necessary.

- A baby presenting with an acute illness - measurement of blood glucose concentration is important to identify hypoglycemia as either the cause or an association of the collapse, and to guide subsequent intravenous fluid management. Unexpected hypoglycemia should alert clinicians to an inborn error of metabolism and appropriate blood and urine samples should be taken immediately, as it is often difficult to diagnose metabolic conditions in normoglycemic, unstressed infants.
- Babies cared for on neonatal units who have known co-existing clinical complications - low blood glucose concentrations indicate that energy provision (intravenous or enteral) should be increased, and monitoring should be continued to assess the effects of changes in management. High blood glucose concentration may be an early marker of infection or other stress which cause metabolic perturbation, and thus alert attending staff to carry out further investigations.

In summary, the determination of blood glucose concentration is essential for the prevention of severe and prolonged hypoglycemia and hyperglycemia, the diagnosis of underlying disorders in sick infants and in guiding feeding and fluid prescriptions for small, vulnerable or sick neonates.

Lactate

Lactate accumulates in tissues, blood and CSF as a result of anaerobic metabolism. Thus, measurement of blood or plasma lactate concentrations gives an indication of the adequacy of recent or current oxygen delivery to tissues which may be reduced during hypoxemia, cardiac failure, or peripheral vascular shutdown.

Whilst bedside monitoring provides an immediate indication of hypoxemia, measurement of lactate concentrations may alert clinicians to problems with oxygen delivery to tissues, for example in neonatal septicemia or persistent ductus arteriosus [2].

High plasma lactate concentrations have been associated with adverse outcome after perinatal hypoxia-ischemia

and in neonates undergoing extracorporeal membrane oxygenation [3, 4, 5, 6].

Finally, measurement of blood and CSF lactate levels is an essential investigation in the diagnosis of inborn errors of metabolism (IEM).

The requirement for accuracy and reproducibility

Glucose

There is now extensive literature regarding the numerical definition of neonatal hypoglycemia, which has been succinctly summarized by Halamek *et al* [7]: "As of 1997 no consensus exists in the normal newborn nursery, NICU, or the courtroom as to the definition of hypoglycemia in the neonate".

Although there can be no single defining values for hypoglycemia and hyperglycemia, many neonatal units aim to maintain blood glucose levels above 2-3 mmol/L and below 10-15 mmol/L in low-birthweight or sick babies.

This range of optimal blood glucose values necessitates accuracy of monitoring, as management may be changed if blood glucose measurements are perceived to change by as little as 1 mmol/L at either end of the optimal range. Inaccurate monitoring may also lead to overtreatment or undertreatment, which may in turn harm the baby.

Lactate

Similarly, blood and CSF lactate concentrations are normally within a narrow range. Mean \pm 2SD for blood lactate concentration for healthy, full-term infants has been reported as 0.22-2.98 mmol/L and 0.26-2.21 mmol/L [8, 9].

Therefore, small deviations from this range may be of clinical significance and methods of measurement must be accurate.

Previous difficulties

Glucose

Leaving aside any controversy regarding definition, it is of greater clinical importance to discuss issues of accuracy of measurement.

Differences arise when comparing plasma and whole blood measurements of glucose, even using accurate laboratory measures [10]. This difference is greater at high hematocrits.

However, as long as either plasma or blood values are consistently used for an individual subject, and method of measurement is reported, the difference between plasma and whole-blood measurements is of lesser clinical significance than the potential inaccuracies of measurement described below.

The most common method used for blood glucose monitoring has been by reagent strip at the bedside, using heelprick capillary blood samples. The perceived advantages of this method are cost, ease of use, accessibility and need for minimal training.

The reagent strips are designed for the detection of hyperglycemia in diabetic patients, for which purpose they are sufficiently accurate. However, it has been demonstrated and the manufacturers themselves acknowledge that reagent sticks have no role in the diagnosis of hypoglycemia because of inherent inaccuracies at low blood glucose concentrations [11, 12, 13].

These problems have been highlighted by the UK Department of Health and the American Academy of Pediatrics [14, 15]. Attempts to introduce more accurate (and more expensive) methods of near-patient glucose monitoring have proved equally disappointing in neonatal practice [16, 17, 18].

If samples are sent to hospital laboratories for accurate measurement to confirm bedside readings, there is the inevitable decline in glucose in a whole-blood sample during transit and delay in reporting a result [18].

Lactate

Until recently, the clinical significance of blood and CSF lactate concentrations has not been widely appreciated by neonatologists, and there has been little commercial drive to produce methods of measurement which may be used outside of specialized or research laboratories.

Therefore, practical limitations of transfer of specimens and reporting time have mitigated against the use of regular lactate monitoring in neonatal practice.

As for glucose, lactate concentrations will change over time in a whole-blood sample because of red-cell metabolism, levels will increase if there is delay in measurement [9, 18].

Recently, methods have been introduced for more immediate and accessible monitoring of lactate concentrations, but these measurements may be available either in isolation or in parallel only with blood glucose measurements.

This limits the value of a single lactate measurement, and the ability to report a lactate concentration alongside simultaneous measurements of glucose, blood gases, and electrolytes (especially chloride) would aid interpretation and add more to the clinical picture.

Future solutions

Neonatologists would not consider embarking upon the care of an infant with respiratory problems without access to rapid and accurate measurement of blood gas values with on-site blood gas analyzers.

In the same way, they would wish to have available an on-site facility for measurement of electrolytes, glucose and lactate in addition to blood gas analysis. Neonatal unit laboratory-based glucose analyzers have been evaluated and have proved preferable to the near-patient methods discussed above [19].

The ability to perform immediate, accurate, and simultaneous analysis of blood gases, electrolytes, glucose, lactate, bilirubin, and hemoglobin or

hematocrit would optimize the management of fluid, salt and energy provision to the smallest and sickest babies in particular.

Analyzers that provide this facility must be:

- Sufficiently robust to handle multiple specimens (and users) and able to function around the clock, with short breaks for maintenance and calibration.
- Have a facility for daily quality control (QC) checks with high and low QC samples appropriate for the neonatal range of concentrations.
- Designed for ease of operation by a multidisciplinary team.
- Amenable to maintenance and basic “troubleshooting” by local medical physicists or biochemists.
- Able to carry out analysis on small specimens.

Clinicians should satisfy themselves that performance data indicate:

- Accuracy, using a recognized “gold standard” measure and employing Bland-Altman plots to interpret data, rather than regression or correlation fits [20].
- The range of measurement is appropriate for the subject group.
- Accuracy at the upper and lower ends of the range of measurement.
- Reproducibility.
- Minimal effects of hematocrit and other factors such as bilirubin concentration.

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