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Continuous glucose monitoring in newborn babies at risk of hypoglycaemia

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In this issue of *The Journal*, Harris et al at the University of Auckland, New Zealand, report results of the application of continuous interstitial glucose monitoring in newborn infants at risk for neonatal hypoglycemia, including late preterm infants (1). This report follows several others with similar observations (2,3,4,5) documenting that in preterm infants, continuously measured interstitial glucose concentrations quite accurately and reliably reflect simultaneous plasma glucose concentrations and are well tolerated. Interstingly, these monitors detect many more episodes of arbitrarily defined "low blood glucose concentration" (≤ 2.6 mmol/L) than are detected by routine, intermittant blood glucose measurements.

At first glance, such observations seem quite exciting. In the proper research settings continuous glucose monitoring in newborn infants would provide much needed data to determine the incidence, severity, and duration of low glucose concentrations, their relationship with symptoms, and their correlation with other pathologies and neurodevelopmental outcomes. Such monitoring also would help discover recurrent episodes of low glucose concentrations that might better predict more serious metabolic diseases, as well as determine when such infants had achieved glucose homeostasis sufficient for safe discharge. In infants requiring treatment for low glucose concentrations, continuous glucose concentration monitoring would have the potential for determining when low glucose concentrations had been corrected, how stable they were during treatment, and when treatment could be safely and effectively discontinued. Previously undiscovered low glucose concentrations, particularly when the rates of intravenous glucose solutions are reduced as enteral feeding is advanced, might show up more clearly. This also might help define whether recurrent low glucose concentrations in preterm infants, such as noted by Lucas et al in 1988 (6), are frequent enough, severe enough, and long standing enough to cause poor neurological development. This would be especially important in preterm infants who, as normal fetuses (7), would have had glucose concentrations consistently above values that Harris et al. and Lucas et al. commonly observed. Continuous glucose monitoring also could reduce the number of blood tests required in infants at risk of hypoglycemia.

Many will want to use continuous glucose monitoring to better define neonatal "hypoglycemia". Hypoglycemia, so far defined by highly variable and unsubstantiated arbitrary threshold lower limit concentrations (8), is the commonest metabolic disorder of newborns and glucose concentration is one of, if not the, most common biochemical measurement in the NICU (9). Severely low and prolonged low glucose concentrations are a preventable cause of brain injury in newborns (10), even if such conditions occur relatively

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infrequently and primarily as a result of metabolic disorders (11). In the low to normal physiological concentration range of glucose, brain glucose uptake and utilization are dependent directly on plasma glucose concentration. A major challenge, however, has been to determine in a given infant the plasma glucose concentration at which brain damage might develop if the glucose concentration falls to lower values and stays low for extended periods. This value, or narrow range of values, probably differs among infants. It also is not known how low, how often, or for how long low plasma glucose concentrations must occur before there is irreversible neuronal damage. Relationships with other pathology also are confusing. There are few data to determine at which values of cardiac output, blood pressure, brain blood/plasma flow, hematocrit, availability of alternative brain energy substrates such as ketones, and relationship to prior or concurrent hypoxic-ischemic conditions (12) a glucose concentration becomes too low for normal brain glucose and energy needs. Furthermore, controversy continues about whether some infants could suffer injury while entirely asymptomatic, as low glucose concentrations in asymptomatic infants often are insufficiently documented. There is not even good information about how best to detect infants at risk of persistent hyperinsulinism or fatty acid oxidation disorders, the leading known causes of permanent brain damage caused by low blood glucose concentrations (13,14,15).

For such reasons, the management of neonatal hypoglycemia currently is based on attempts to detect low glucose concentrations in infants at risk and the maintenance of blood glucose concentrations above a presumed likely safe level. As noted by Harris et al, such detection involves intermittent blood sampling, which is invasive and painful, sometimes technically challenging, and may miss episodes of low glucose concentrations for periods long enough to potentially cause neuronal injury. It also leads to unnecessary treatment of infants who would tolerate lower glucose concentrations without adverse consequences, such as healthy breast fed infants, or who experience only transient low glucose concentrations, which according to several reports are common for many days after birth (2). Intermittent glucose measurements, therefore, could miss detection of infants with glucose concentrations low enough for long enough to threaten brain function, or lead to inappropriate and invasive treatment in infants who are at no risk of impaired brain function with only an occasional decrease in plasma glucose concentration.

At first glance, therefore, it seems entirely reasonable that continuous glucose monitoring would be a valuable tool at the bedside of individual infants. In fact, it already is popular in the management of diabetes, and may improve metabolic control in patients with trauma, surgery, or severe medical illnesses in the intensive care unit (although in such settings, it has been used primarily to reduce potential complications of hyperglycemia, not just prevent or correct hypoglycemia) (16). The need for such monitoring in infants has been a constant challenge, of national and international importance. For example, a recent report from a workshop organized by the Eunice Kennedy Shriver National Institute of Child Health and Human Development on “Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia” developed a “Research Agenda”, which included the need to “Determine long-term outcomes in neonates with asymptomatic hypoglycemia, focusing on subtle neurocognitive outcomes including executive functions” and to “Determine the effects of the frequency, severity, and duration of episodes of low plasma glucose” (17). Clearly these research goals will be accomplished much more effectively with continuous glucose monitoring.

Do such observations support continuous glucose monitoring in neonates? On further consideration, there is reason for caution. Continuous glucose monitoring will fundamentally alter how data on glucose concentrations are acquired and interpreted, changing an “intermittent” variable to a “continuous” one. This will challenge clinicians with new sets of problems related to low glucose concentrations. For example, recent clinical trials of insulin

infusion in very low birth weight neonates showed that continuous glucose monitoring detected many more episodes of low glucose concentrations than standard intermittent blood glucose measurements (5). There is no information about the clinical significance of these episodes of low interstitial glucose concentrations and which, if any, should be treated, or in which infants. There is real danger, therefore, that continuous glucose monitoring might be incorporated into clinical practice without critical assessment and might result in many more infants being treated than would be necessary. Additionally, if continuous interstitial glucose monitoring devices are used before rigorous research data determine which glucose concentration (and of what duration) to use as a lower limit threshold for clinical management, there is considerable potential that low glucose concentrations might engender even more law suits than already exist. Such concerns support the need for studies to clarify the relationships between continuous glucose concentrations in the newborn, symptomatic hypoglycemia, response to treatment, associated medical conditions, and longer term neurodevelopmental outcomes. The importance of such studies must be balanced against a delay in implementation of this technology and its potential to detect serious, recurrent hypoglycemia in patients with hyperinsulinemic hypoglycemia and other metabolic disorders.

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