CONTROVERSY

Prevention and management of neonatal hypoglycaemia

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How do normal neonates adapt to extrauterine metabolism?

When the umbilical cord is clamped, the neonate faces a metabolic problem: the insulin dominated fetal milieu, so essential for fetal growth,^{1,2} must be terminated to prevent extracellular glucose from disappearing into fat and muscle, to the detriment of the brain. After birth, residual fetal insulin precipitates the sharp decline in plasma glucose concentration in the first neonatal hour.³ The nadir occurs in the second hour when the combined effect of counter-regulatory hormones (adrenaline⁴ and glucagon^{5,6} suppress insulin dominance (fig 1). These hormones raise the plasma glucose concentration above the nadir by 3–4 hours of age.

The concept of 'sensor failure' provides a useful framework to explain the persistence of a low plasma glucose concentration in some infants and may result from one or more of the following: sensor immaturity (preterm infants), altered preset (maternal hyperglycaemia), malactivation during delivery (anoxia induced), or antenatal activation (intrauterine growth retardation). Sensor failure results in a two hour plasma glucose concentration which continues to fall and the infant comes to medical attention because of symptoms or screening. Their management is controversial in 1994^{7–11} but it is reasonable to assume that a symptomatic infant with a persistent plasma

glucose concentration of 0–1 mmol/l has an increased risk of brain damage.¹² There is no consensus, however, when attempts are made to coopt values between 1 and 3 mmol/l to establish a 'safe working threshold' for all infants.

This review presents an alternative view which reduces the reliance on threshold values and has two aims:

- (1) To show that maladaptation of perinatal endocrine control, by generating a transitional endocrine state, is the primary cause of most neonatal hypoglycaemia.
- (2) To formulate practical recommendations based on this model which are sufficiently robust to manage different aetiologies.

Supply and demand of neural fuel**ENDOCRINE ADAPTATION TO BIRTH AND THE ROLE OF INSULIN**

Three aspects of the neonate's adaptive response^{4,13–16} have been selected: neural energy supply, glucose competition, and the provision of ketones as neural fuel.

(1) Regulation of brain energy supply

At birth anoxia, cord clamping, and tactile stimulation⁴ signal the need for cerebral fuels¹⁷ to the liver and pancreas via an adrenergic mechanism.⁴ The adrenergic response suppresses insulin release (fig 2) and stimulates glucagon secretion. In the splanchnic bed, the resultant low insulin/high glucagon environment is a prerequisite (figs 3 and 4) for the hepatic synthesis of two neural fuels (glucose and ketone bodies).¹⁴ Neither may be synthesised in the presence of insulin¹⁸ because of (i) inhibition of the hepatic enzymes mediating gluconeogenesis and ketogenesis and (ii) a reduced supply of substrate: amino and fatty acids from muscle and adipocytes respectively¹⁸ (see fig 5). Thus the primary function of glucagon is to ensure supply of fuels capable of being utilised by the brain. This is why the highest physiological concentrations of adrenaline and glucagon are found immediately after birth^{6,16,4} Furthermore infants with congenital or acquired glucagon deficiency^{19–22} have near zero plasma concentrations of glucose and ketone bodies.

The perinatal effects of glucagon were investigated as early as 1969 when Blum *et al*

Figure 1 Glucose homeostasis in the immediate postnatal period in a cross section of normal term infants. The putative normal range of plasma glucose concentration is shown between the bold lines. The shaded rectangle indicates the region of controversy with respect to necessity and mode of treatment. (Term, normal range from Srinivasan *et al.*³)

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Glucose transporters

Glucose transporter	Tissue distribution	Special properties
GLUT 1*	Red cells, placenta, brain, and blood-brain barrier	May be asymmetric one way glucose valve
GLUT 2	Liver (plasma membrane), pancreatic β cell,† intestine	High capacity – 50% saturated at 50 mmol glucose
GLUT 3*	Brain, placenta, heart	No insulin effect
GLUT 4†	Fat and muscle, not in brain	Insulin increases transporter numbers by 15 to 20-fold
GLUT 5	Small intestine (brush border)	Fructose transporter
GLUT 7 (see GLUT 2)	Liver, endoplasmic reticulum	Part of glucose-6-phosphatase, glucagon enhanced

*Found in different cell types within the brain. †Active in insulin induced hypoglycaemia.
‡Forms part of the glucose sensor: ensures glucose uptake is linear with respect to concentration in portal vein.

studied 34 small for dates neonates and 31 controls in the first three days of life.²³ They found that both groups responded rapidly to intravenous glucagon with mean increments in plasma glucose concentration above 3 mmol/l and commented that ‘glycogenolysis is available but not called into action, even in the presence of very low levels of circulating glucose’.

(2) *How does glucose get into the brain?*
Glucose enters cells via transmembrane proteins (GLUT, glucose transporter) with divergent tissue distributions (table). Insulin

Figure 2 Biology of β cell insulin secretion. The stippled areas represent two pancreatic β cells. The upper cell is responding to glucose by reducing potassium exit, which triggers calcium (Ca) dependent insulin release. Diazoxide reverses glucose stimulation. The lower cell shows the effects of perinatal adrenaline, which augments potassium (K) exit and inhibits insulin secretion. Note that the adrenaline gated K channel is different from the diazoxide channel in the upper cell.

activates the transporter found in muscle and fat but brain uptake is for the most part insulin independent and occurs by the sequential transport of plasma glucose first (via GLUT 1) in the blood-brain barrier²⁴ into the cerebrospinal fluid and second (via GLUT 3) across the plasma membrane of human neurones. There are in vitro data showing that GLUT 1 would be fully active at a plasma glucose concentration of 3 mmol/l but largely inactive at 1 mmol/l (G W Gould, Department of Biochemistry, University of Glasgow, personal communication). In contrast, the neuronal transporter GLUT 3 (which sees only cerebrospinal fluid glucose) has the potential to be active at a cerebrospinal fluid glucose concentration of 1 mmol/l, a tandem arrangement ensuring the ‘downhill’ flow of glucose to the inside of a brain cell. It is pure speculation to use these arguments to suggest that a plasma glucose concentration of 3 mmol/l is safer than 1 mmol/l, the determination of the concentration-activity values for GLUT 1 in vivo is awaited. In the area of maximal clinical controversy, a plasma glucose concentration of 1–3 mmol/l, those neurones with the lowest GLUT 3 activity/number relative to demand would be the first to malfunction as cerebrospinal fluid glucose concentration declined. In contrast, those neurones expressing enzymes for the utilisation of ketone bodies would have the capacity to switch fuels and reduce glucose demand. If both fuels are in short supply (for example, the infant of a diabetic mother when insulin activity is unopposed; see fig 5) brain damage will be more likely to occur – no other exogenous fuel is utilised by the neonatal brain.

(3) *Unique role of ketone bodies in the neonatal brain*
The neonatal brain has an enhanced capacity to utilise ketone bodies relative to infants (fourfold²⁵) and adults (40-fold²⁶). As much as 12% of acute neonatal energy needs may be met from beta hydroxybutyrate and acetoacetate, rising to 30% with prolonged fasting.²⁵ This observation alone makes the debate about the relative dangers of threshold values of plasma glucose concentration rather sterile unless ketone flux is considered. The presence of ketones in the 0.1–0.5 mmol/l range is a good indication that neonatal adaptation is taking place, that is insulin activity is low. Ketone body concentration is extremely sensitive to insulin inhibition and values in the 0.01 mmol/l range are better markers of insulin activity than insulin or glucose concentration.

Management of hypoglycaemia
(A) PREVENTION OF HYPOGLYCAEMIA
The use of intravenous dextrose in the (non-diabetic) mother during labour also increases the incidence of neonatal hypoglycaemia.²⁷ If local obstetric practice requires dextrose to augment resistance to maternal exhaustion, its

rate of administration should be adjusted so as not to produce maternal hyperglycaemia. Dextrose is doubly dangerous when β adrenergic agonists are used to arrest labour as they increase fetal insulin release.²⁸

Figure 3 Generation of neural fuel after birth. The stippled area represents a liver cell bathed in high concentrations of insulin and glucagon on its portal surface. Glucagon's role in regulation of the direction of metabolic flux is illustrated but note that glucagon cannot operate in the presence of insulin. The consequences for neural integrity are shown in figs 4 and 5.

Figure 4 Metabolic adaptation to fasting (high glucagon, low insulin state). The well adapted neonate utilises glucagon to drive hepatic fatty acids into ketone production. Glucagon reduces the intrahepatic concentration of an inhibitor of gluconeogenesis as well as stimulating its key enzymes. The acetyl CoA by-product of fatty acid oxidation is used as an energy source for gluconeogenesis. (CSF=cerebrospinal fluid.)

(B) DETECTION OF HYPOGLYCAEMIA

Reagent impregnated stick tests were never designed for neonatal use, are known to be imprecise between 0 and 3 mmol/l – the critical range for acute neural dysfunction,⁹ and underestimate the true value more often than they provide false reassurance of a normal plasma glucose concentration.⁸ Thus in 1994 infants are subjected to unnecessary treatment (false positives) or left languishing on postnatal wards with undiagnosed hypoglycaemia (false negatives). If the latter subsequently undergo delayed development, hypoglycaemia may not even be recorded as a potential cause. Cornblath and Schwartz recommend that their use, whether read by eye or meter, should be treated as a screening exercise.⁸ If the result is below 3 mmol/l, rapid confirmation against a laboratory value is mandatory. This recommendation should be implemented immediately. Optimal treatment will then require the provision of facilities for laboratory results within five minutes of the sample being taken, that is nursery nurses will need to be instructed on the use of a whole blood glucose analyser (the Yellow Springs instrument is the best).

In the following sections it is impossible to cover every hypoglycaemic scenario. I have therefore concentrated on principles which may be extended to the management of all infants irrespective of gestational age, excluding those with inborn errors of metabolism or hypopituitary states.

(C) MANAGEMENT OF DIFFERENT GROUPS OF NEONATES

(1) Hypoglycaemic term infants – rare and difficult to diagnose

Asymptomatic infants with a plasma glucose concentration between 1 and 2.5 mmol/l hardly ever come to the attention of doctors. They are fed with milk and make a successful transition to postnatal life. In the absence of symptoms, counter-regulation is likely to be active but there is no gold standard definition of the asymptomatic state. It is reasonable to assume that if ketone body concentrations are around 0.5 mmol/l, insulin activity is low. Unfortunately automated ketone measurements are not routinely available despite easy assay techniques.

(i) Treatment plan (actions to be taken in **bold type**) – thus no treatment is necessary unless:

- (1) The plasma glucose concentration is 0–2 mmol/l (fig 1).
- (2) The infant is symptomatic (unexplained lethargy, cyanosis, irritability, or fits) with a plasma glucose concentration below 3 mmol/l (arbitrary value which will include some false positives from other causes, a lower value will miss some infants).

(3) The infant remains 'white' after delivery, indicative of blood loss and flow diversion to essential organs²⁹ (the diving reflex), that is potentially away from the splanchnic part of the glucose sensor (for example antepartum haemorrhage, the donor in twin-twin transfusion syndrome – especially if hypoxia is present).

Figure 5 Hypoglycaemic infant (high insulin, low glucagon state). The consequences of failed adaptation – insulin prevents release of the precursors of gluconeogenesis and ketogenesis. Glucagon can no longer activate the key enzymes of gluconeogenesis.

In (1) counter-regulation has failed. In (2) counter-regulation may have failed if the plasma glucose concentration is between 1 and 2 mmol/l after four hours of life. In (3) counter-regulation may be inadequate (**monitor plasma glucose concentration**).

ACTION: In (1) and (2) above, take 3 ml of baseline blood (preferably arterial, see later) at presentation and store it for later analysis of insulin, glucose, ketones, glucagon, cortisol, triiodothyronine, growth hormone, electrolytes and packed cell volume before treatment is started. It is essential to have sets of bottles containing preservative made up in the refrigerator: THE BLOOD MUST BE KEPT ON ICE AND THE PLASMA FROZEN RAPIDLY. Retrospective analysis is the only way not to miss rare metabolic and endocrine causes.

ACTION: In (1) – (3), an intravenous glucose infusion should be given at a rate not exceeding 5 mg/kg/min (10% dextrose is 100 mg/ml).

(ii) *Justification for low infusion rates of dextrose* – On no account should boluses of dextrose be given – they inhibit glucagon secretion.^{13 16 30} A fasted adapted infant produces the hepatic equivalent of 0.05 ml of 10% dextrose/kg/min³¹

(that is 3 ml of 10% dextrose/kg/hour). Thus in a 3000 g neonate, 1 ml of 10% glucose (100 mg glucose) should remain in the circulation for a minimum of seven minutes. Boluses exceed the capacity of the brain to utilise glucose and the excess stimulates the pancreatic β cell. There are two further detrimental effects (i) each succeeding bolus decreases the threshold for insulin release by the pancreatic β cells, producing a positive feedback loop¹⁶ and (ii) a raised glucose concentration itself depresses hepatic glucose release,^{32 33} thus buying short term gain at the expense of prolonging dependence.

Anatomical considerations alone suggest that the use of boluses of glucose are inappropriate because the lung alveoli are the only significant consumers of glucose lying in series between the site of glucose infusion (arm or leg vein) and the brain (this also explains the anatomical location of the liver which is strategically placed to supply glucose to the brain without competition from peripheral muscle and fat). Thus the anatomical site where glucose is measured (arterial versus venous) provides different data about whole body glucose dynamics. One of the major problems with current treatment is over-reliance on venous glucose results. This blood has been exposed to insulin dependent glucose transporters of the muscle and fat cells (see later and table). Capillary samples are not much better as they often have to be squeezed from badly bruised heels. Clinically, misinterpretation of venous plasma glucose concentration produces a vicious cycle of increments in dextrose infusion rate unmatched by a sustained rise in venous glucose concentration (as insulin increases the number of GLUT 4 molecules and drives glucose into fat and muscle). The use of arterial measurements avoids this pitfall but is more difficult.

(iii) *Monitoring treatment: one hour after intravenous dextrose*

Result 3a (arterial). If arterial plasma glucose concentration is less than 2.5 mmol/l, a best

Figure 6 A 3000 g term infant with symptomatic hypoglycaemia treated with glucose boluses and oral feeds. Glucagon was administered while oral and intravenous (IV) feeds were continued (total glucose administration rate 12–15 mg/kg/min). This manoeuvre only raised glucose concentration for a few hours and a sustained response only occurred when oral feeds were stopped and the stomach emptied.

guess value, the dextrose infused into the venous blood is being diluted with glucose poor blood from the liver.

ACTION 3a: Give glucagon (200 µg/kg intravenous bolus) to increase hepatic glucose production and stimulate gluconeogenesis and ketogenesis.

Result 3v (venous). If only venous results are available: provided fetal insulin is suppressed, 5 mg/kg/min of dextrose (3 ml/kg/hour 10% dextrose) should result in a venous plasma glucose concentration >2.5 mmol/l. Reduce the dextrose rate (0.5 ml/kg/hour) and introduce feeds as clinically indicated.

If insulin suppression has failed, venous plasma glucose concentration will either be unchanged from the initial low value or fail to rise above 2.5 mmol/l (best guess value – no good data).

ACTION 3v: Give glucagon 200 µg/kg intravenous bolus – this will produce sustained pharmacological concentrations for at least 12 hours.

Term infants often present beyond the first 24 hours of life.^{34 35} A glucose infusion of 5 mg/kg/min will nevertheless sort out those who have excess insulin activity from the remainder. Rarely, even these measures will fail to suppress insulin release for more than a few hours and diazoxide (5 mg twice a day, adrenaline (500 ng/kg/min) and hydrocortisone (20 mg), or somatostatin (2–5 µg subcutaneous) may be needed prior to further glucagon administration. Future work needs to be directed to the detection of defects in gluconeogenesis under these circumstances.³⁶

(iv) What if glucose boluses have been given? – Such infants will be hyperinsulinaemic and hypoketonaemic – give intravenous glucagon immediately – preferably in the referring hospital before transfer. They have often had several days of hypoglycaemia, have usually been fed, and gain only temporary relief with glucagon (fig 6). It is essential that the stomach be emptied with a nasogastric tube to remove residual milk and no feed should be given until low glucose infusion rates achieve venous normoglycaemia (A Mehta, unpublished observations; see fig 6 for typical time course). Speculation: milk induced, gut hormone release (? gastric inhibitory polypeptide or amino acid stimulation) augments portal insulin activity beyond the capacity of glucagon to reverse it. Some are suspected of having nesidioblastosis but this may be iatrogenic (perhaps on a genetic background,³⁵ induced by non-physiological, sustained, insulin induced islet hyperplasia after repeated glucose boluses and oral feeds.

(2) Infants of diabetic mothers – common and symptomatic

These infants are deficient in perinatal catecholamines.³⁷ They fail to undergo the normal glucagon surge in the first few hours of life, despite hypoglycaemia,³⁸ and have inadequate hepatic glucose production. Glucagon boluses (300 µg/kg), given immediately after birth have been shown to improve glycaemic control (reviewed elsewhere⁸). Peripheral glucose uptake is enhanced and endogenous (hepatic) glucose release suppressed producing an increased glucose requirement of up to 10 mg/kg/min. The purpose of glucagon treatment is to reduce the dependence on intravenous dextrose and shorten the time to full oral feeding. This treatment complements and is not a substitute for early oral feeds.

(3) Growth retarded infants – mixed and mismatched

Hypoglycaemia is common and may be compounded by a lack of substrate for ketogenesis.³⁹ Clinically, these infants are devoid of fat either because they never acquired it (early, proportionate retardation for head, weight, and length) or lost it in later gestation (weight << length and head) as placental supply failed. The latter are mismatched between supply and demand and may well already have activated gluconeogenic enzymes to supply the brain in utero; however, gluconeogenesis cannot work without its energetic drive mechanism (acetyl CoA derived from fat¹⁸).

Postnatally, these thin hungry babies will raise their plasma glucose concentration with non-glucose substrate (glycerol or medium chain triglyceride) which supplies energy for gluconeogenesis. However, hyperinsulinism has also been found in 50% of this group, particularly when they are subjected to perinatal asphyxia⁴⁰ when they may need insulin suppression using the protocol for term infants.

(4) Preterm infants – a new problem

Hypoglycaemia is never an acute problem in these infants as they are nearly always given intravenous glucose within the first hours of life and never undergo a period of hypoglycaemia. The effect of intravenous glucose on an underdeveloped/developing glucose sensor is unknown but the frequent occurrence of hyperglycaemia may indicate a defect. Hypoglycaemia occurs if they are not fed, but the indications for hormonal manipulation are unclear because of the confounding effects of treatment. It is known that steroids are needed to prime the adrenergic response to birth and their antenatal administration is quite common. The effect of these drugs on glucose recycling needs evaluation.^{41 42}

The protocol outlined above will need to be subject to clinical trial and a number of clinical questions remain to be answered:

(1) Does the administration of early intravenous glucose produce neonates who are maladapted to intermittent feeding?

(2) Will glucagon administration improve the subsequent adaptive response?

(3) Will enhanced ketone availability have measurable effects on neurodevelopment?

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Commentary

Dr Mehta's paper outlines many theoretical concepts which complement the more practical and pragmatic approach of our paper. More specifically, he agrees that ketone bodies may be important neonatal fuels especially for the brain, and that both neonatal hypoglycaemia and failure of ketone body production arise as a result of the failure of neonatal metabolic adaptation. In practical terms there is also agreement between us regarding the difficulties of definition, the avoidance of a rigid 'cut off' level, and the necessity for rapid accurate diagnostic methods without depending on reagent test strips. In terms of treatment of hypoglycaemia we agree that it is inadvisable to use high rates of glucose infusion or large intravenous boluses and that glucagon may be a useful additional treatment.

However, we feel that pragmatic recommendations are needed for the benefit of nursing and medical staff and that theoretical issues should be viewed in this context. Dr Mehta over emphasises the role of hyperinsulinism in the aetiology of neonatal hypoglycaemia. We have recently demonstrated that, especially in babies with disordered blood glucose homeostasis, there are poor relationships among circulating blood glucose concentrations, plasma insulin concentrations, and glucose production rates. In addition, blood ketone body concentrations and plasma non-esterified fatty acid concentrations were not related to plasma insulin concentrations.^{1,2} This is not surprising in view of the many other factors which are essential for glucose and ketone body production, namely substrate availability, counter-regulatory hormones, and induction of enzyme systems.³

The main area of controversy regarding management appears to be in the treatment of the asymptomatic term infant whose blood glucose concentration is <2.0 mmol/l. Dr Mehta has already suggested that the presence of ketone bodies may protect the brain and our paper out-