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ORIGINAL PAPER

Hypothesis: proposals for the management of a neonate at risk of hyperammonaemia due to a urea cycle disorder

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Abstract It is difficult to prevent hyperammonaemia in patients with urea cycle disorders that present in the newborn period. This is true, even if treatment is started prospectively because of an affected relative. We propose several additional measures that could be used in conjunction with conventional therapy to improve the metabolic control. Catabolism could be reduced by delivering the babies by elective caesarean section, by starting intravenous glucose immediately after delivery and, possibly, by using β-blockers or octreotide and insulin. The effectiveness of sodium benzoate and sodium phenylbutyrate might be increased by giving phenobarbital to the mother before delivery and subsequently to the baby to induce the enzymes for conjugation. We would expect the proposed measures to reduce the risk of hyperammonaemia and to improve the outcome for these patients. They have not, however, previously been used in this context, so families would need to be counselled carefully and controlled studies should be undertaken.

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Abbreviations

ACTH	Adrenocorticotrophic hormone
CPS	Carbamyl phosphate synthetase
ECMO	Extracorporeal membrane oxygenation
NAG	N-aceylglutamate
OTC	Ornithine transcarbamylase

The prognosis for urea cycle disorders presenting in the neonatal period is generally poor [16, 24]. In one small study, results were less bad for a heterogeneous group of patients that included organic acidaemias [18]. Other studies have suggested that even moderate hyperammonaemia is very commonly associated with a poor outcome [3, 14, 17]. The outcome of urea cycle disorders has recently been reviewed [6]. Until more detailed information is available about ways of reducing the morbidity and mortality, every effort should be made to keep the plasma ammonia concentration as low as possible. It is, however, unusual to make the diagnosis clinically before the patient already has marked hyperammonaemia (> 400 μmol/l).

Prospective treatment is possible if a baby is known to be at risk of neonatal hyperammonaemia because of the family history. The history will generally be of hyperammonaemia in a sibling but, for ornithine transcarbamylase deficiency, more distant relatives are relevant. Outcomes have always been better for prospectively treated patients [15]. Nevertheless, it can still be difficult to keep the plasma ammonia concentration below 400 μmol/l with conventional therapy, even if started prospectively. This is particularly true for carbamyl phosphate synthetase (CPS)

deficiency (OMIM #237300) and ornithine transcarbamylase (OTC) deficiency (OMIM #311250).

In this paper we suggest some new ideas about management of babies at risk of having a urea cycle disorder that may help to control hyperammonaemia.

Metabolic events around the time of birth

In utero, the fetus receives a constant supply of glucose, which crosses the placenta down a concentration gradient, facilitated by the GLUT1 glucose transporter. Fetal insulin concentrations are high and glucagon concentrations are low [12]. Around the time of birth, babies show a number of hormonal changes. First, catecholamines and cortisol are released in response to the stress of the birth process. Subsequently, there is the hormonal response to the interruption of the supply of glucose from the placenta. This response has two phases: within the first postnatal half-hour, the physiological fall in the blood glucose concentration triggers a surge in the glucagon concentration and a fall in the insulin concentration [12, 22]. There is then a more prolonged phase of catabolism, the severity of which depends on the length of time to reach adequate volumes of feed.

These changes increase the rate of proteolysis, gluconeogenesis and the urea cycle so that inborn errors of catabolic pathways commonly present in the immediate post-natal period, even if milk feeds are withheld.

Investigations

Investigation of the new baby is simplified if the diagnosis is known in the index case. If the index case died, the diagnosis may be uncertain: further studies should be undertaken urgently if appropriate samples have been saved.

If there is a risk of neonatal hyperammonaemia, it is extremely helpful to know whether the baby is affected *before birth* so that appropriate plans can be made. Affected babies should be transferred *in utero* or soon after delivery to a centre with facilities for full intensive care, whereas babies known to be unaffected can stay locally and be treated normally. If prenatal diagnosis has not been undertaken earlier, the mother may agree to amniocentesis late in pregnancy. In some cases, however, it is not possible to determine whether the fetus is affected (for example in CPS or OTC deficiencies if molecular genetic studies have not been undertaken on the index case). In these cases, serial ammonia measurements and specific tests will be needed following delivery.

Management

Intensive care

The standard management of a hyperammonaemic neonate is discussed elsewhere [23] and will only be summarised here. As any patient at risk of severe hyperammonaemia may deteriorate rapidly, careful thought should be given to their transfer to ICU. If there is any doubt, patients should be ventilated electively with good vascular access, usually via a multi-lumen central line. Initially babies may be dehydrated but rehydration should be cautious because of the sodium load from the medication and the risk of cerebral oedema.

Feeding and intravenous therapy

Milk feeds are probably less significant than endogenous catabolism in precipitating hyperammonaemia. Nevertheless, protein should be withheld initially in a baby at risk of a severe urea cycle disorder (i.e., if the index patient presented within the first few days). Unless there is severe hyperammonaemia (>200 μmol/l), however, some milk should gradually be introduced, starting within about 48 hours of birth. Withholding protein for longer will only exacerbate the catabolic state.

If the index patient presented after the first week, the new baby should be given the minimum safe level of protein intake from birth (approximately 1.5 g/kg/day). Breast feeding should be allowed under these circumstances with top-up feeds of a low protein formula over the first 48 hours to minimise catabolism. It is particularly difficult to decide on the intake for females with OTC deficiency as the severity of their disorder cannot be predicted: a few females with unfavourable lyonisation will develop neonatal hyperammonaemia. Careful monitoring of the plasma ammonia concentration is essential, and if there is any doubt treatment with drugs should be started (see below).

Prevention of catabolism: Mode of delivery

The stress of birth is the first perinatal stimulus to catabolism, associated with the release of cortisol and catecholamines. Hyperammonaemia does not occur till a number of hours after delivery but once catabolism has started it may be difficult to reverse in babies with severe urea cycle disorders. Delivery by an elective caesarean section is associated with lower catecholamine and cortisol levels compared to vaginal delivery [4] and this is the only process known to reduce the stress associated with being born. If a fetus is known to have a severe urea cycle disorder, the option of elective caesarian section should be discussed with the parents, along with the plans for

subsequent neonatal management, so that they can make an informed choice.

Prevention of catabolism: Intravenous glucose

The next stimulus to catabolism is the fall in blood glucose once the placental supply is interrupted. This stimulus to catabolism could largely be prevented by an intravenous infusion of glucose at 6 to 8 mg/kg/min. The infusion would, however, have to start *immediately* after delivery, for example, through an umbilical catheter, because the hormonal mediators of catabolism are released with 30 minutes of delivery (see above). Though glucose can be given orally (for example, as a soluble glucose polymer), it is not possible to rely on the intake being sufficient to prevent catabolism completely. Moreover, small babies may only tolerate relatively small quantities without developing diarrhoea. If hyperglycaemia develops, it is important to start an insulin infusion rather than cutting back on the glucose infusion. The energy intake could be increased by adding a fat emulsion, either orally or intravenously. Long chain fatty acids are important in activating carnitine palmitoyltransferase type I, the rate limiting step in β-oxidation. Fat emulsions have not been used extensively in neonates with inborn errors but they should be safe in urea cycle disorders.

Pharmacological prevention of catabolism

There have been no published reports of babies with urea cycle disorders managed prospectively with all the aggressive strategies discussed above. It is, therefore, uncertain whether these measures will completely prevent catabolism. Moreover, there will be some cases in which these measures cannot be implemented fully. It would, therefore, be helpful to have drugs that could prevent catabolism. Adrenergic blockade has been shown to reduce catabolism in patients with severe burns [8] and it may have a role in neonates with inborn errors of metabolism.

We have already mentioned the need for insulin if glucose infusions lead to hyperglycaemia. There may also be a role for octreotide combined with insulin. Octreotide is a long acting analogue of somatostatin: both agents suppress insulin secretion and octreotide is now widely used for the neonatal and long term management of congenital hyperinsulinism [10]. It is given as a continuous subcutaneous (or intravenous) infusion in doses of 5–25 mcg/kg/day and it appears to be safe in these babies. Octreotide suppresses the secretion of glucagon, growth hormone and ACTH in addition to insulin. If given alone, octreotide would probably increase protein catabolism by lowering insulin levels. If it is combined with infusions of glucose and insulin, however, octreotide is likely to suppress protein catabolism because of its effects on glucagon, growth hormone and cortisol. Evidence supporting this has been obtained in adults with multiple organ dysfunction syndrome [2].

N-carbamylglutamate

Flux through the urea cycle is regulated by the synthesis of N-acetylglutamate (NAG), an allosteric activator of CPS. NAG synthase deficiency is a rare cause of neonatal hyperammonaemia but an important one to consider, because patients respond to treatment with N-carbamylglutamate, an analogue of NAG [21]. N-carbamylglutamate can also lower ammonia concentrations in some patients with partial CPS deficiency and organic acidaemias [5, 13]. If a neonate has died of hyperammonaemia without these conditions being excluded, N-carbamylglutamate should be given to future siblings, either prophyllactically from birth or immediately if ammonia concentrations start to rise.

Alternative pathways for nitrogen excretion: inducing the enzymes of conjugation

Large doses of arginine are used in patients with citrullinaemia and argininosuccinic aciduria to promote nitrogen excretion as citrulline or argininosuccinate. Sodium benzoate and sodium phenylbutyrate (or sodium phenylacetate) are used in all severe urea cycle disorders to exploit alternative pathways for nitrogen excretion [23]. At the recommended doses, these drugs appear to be safe and reasonably effective in older subjects. There are, however, few published data about plasma concentrations, the rates of conjugation and nitrogen elimination in neonates. Neonates are usually given loading doses followed by continuous infusions. Despite these, the available data suggest that maximal rates of conjugation are not achieved for several days. Figure 1 shows the concentrations of ammonia, benzoate and hippurate over the first two weeks in a neonate with argininosuccinic aciduria: maximal hippurate concentrations are only reached on day 9. The conversion of benzoate to hippurate depends first on benzoate:CoA ligase and then on benzoyl-CoA:glycine N-acyltransferase. In neonatal rodents, these enzyme cannot be induced by benzoate itself but they can be induced by phenobarbital [1, 19]. The rate of conjugation in neonates with urea cycle disorders might, therefore, be increased by giving phenobarbital as well as sodium benzoate. Phenobarbital has been used extensively in neonates but its use in this context should, of course, be closely monitored to establish whether the observations in rodents are also true in humans.

Ideally, one would like the conjugating enzymes to have maximal activity at the time of birth. It may be possible to

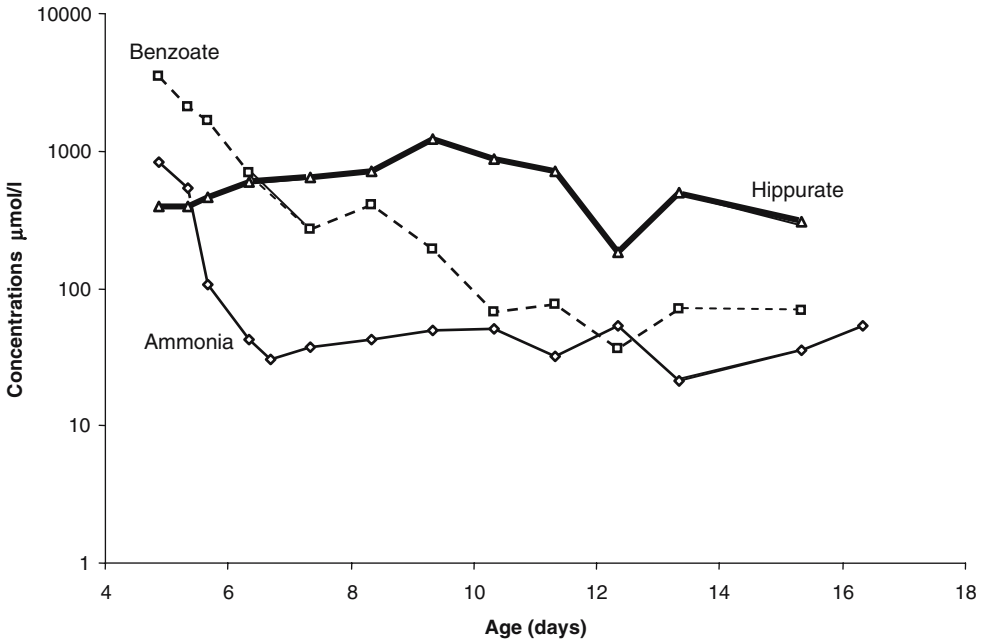

Fig. 1 Serial concentrations of ammonia, benzoate and hippurate over the first two weeks in a neonate with argininosuccinic aciduria. Concentrations are on a logarithmic scale

achieve this by inducing the enzymes in utero. If phenobarbital induces increased activity of benzoate:CoA ligase and benzoyl-CoA:glycine N-acyltransferase in neonates, it might also induce increased activity before birth. It might, therefore, be helpful to give the mother phenobarbital for a few days before delivery if the fetus is known to have a severe urea cycle disorder. Phenobarbital has been given to mothers in the past to induce the conjugation of bilirubin in neonates, before the introduction of phototherapy simplified the management of neonatal jaundice [20]. Obviously, the use of phenobarbital would need careful monitoring and the experimental nature of this treatment should be discussed fully with the family. Sodium benzoate appears not to induce its enzymes of conjugation but sodium phenylbutyrate may do so, as it induces the expression of many genes [11]. If phenylbutyrate can be shown to induce its own conjugation, it may be helpful to give the mother this drug as well as phenobarbital.

Dialysis

Early diagnosis and intensive therapy are important and, if the metabolic disturbance cannot be controlled quickly, dialysis should be started early. The various alternatives for dialysis have been reviewed elsewhere [23]. ECMO/haemodialysis and haemodiafiltration are the most effective [7, 23] but they are technically more demanding. Although somewhat less effective, continuous veno-venous haemofiltration is widely available and less likely to cause serious complications [9]. Peritoneal dialysis lowers ammonia concentrations more slowly. Exchange transfusion has no place in the management of hyperammonaemia.

Neuroprotection

Various forms of treatment have been proposed to reduce the adverse effects of hyperammonaemia on the brain. Potential neuroprotective measures include hypothermia [26] and NMDA receptor antagonists, such as memantine [25]; their effectiveness is not yet clear. Obviously, trials should be undertaken in patients with established hyperammonaemia before they can be justified in those at risk of hyperammonaemia.

Conclusions

With standard treatment, it is often difficult to control hyperammonaemia in patients with severe urea cycle defects presenting in the newborn period, particularly CPS and OTC deficiencies. We suggest some additional measures that may help to control plasma ammonia concentrations. The measures we propose include giving the mother phenobarbital for a few days before delivery, delivering the baby by an elective caesarean section and managing the baby aggressively, with intravenous glucose from birth and drugs started soon afterwards. Several of these ideas have not yet been tried so that controlled studies need to be done to confirm that they are both safe and effective. Obviously, the situation needs to be discussed fully with the family in advance and a detailed management plan needs to be agreed by the metabolic specialist, obstetrician and neonatologist. It is likely that the some of the proposals are also applicable to other disorders that present with early decompensation in the neonatal period, such as organic acidaemias.

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