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Malcolm I Levene

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Cool treatment for birth asphyxia, but what’s next?

Malcolm I Levene

Recently published studies have confirmed that moderate hypothermia for 72 h after severe birth asphyxia reduces death and disability 1–3 and the Treatment of Perinatal Asphyxial Encephalopathy (TOBY) study has also shown that the number of ‘normal’ infants surviving birth asphyxia at term is significantly increased by this treatment.5 In the UK most paediatricians appear to feel that hypothermia is now a standard of care for severely asphyxiated infants. Research into hypothermia was stimulated by increased understanding of the neurobiology of brain injury occurring after a global hypoxic-ischaemic insult. For a review of neonatal brain protection see Gressens.4 Despite the remarkable beneficial effects of hypothermia, improvement in subsequent outcome of asphyxiated babies is probably only improved by about 30% and it is likely that other neuroprotective therapies may add incrementally to the proven benefit of hypothermia. Indeed hypothermia may buy additional time for neuroprotective drugs to act within an expanded ‘therapeutic window’. This review article considers a number of potentially neuroprotective drugs on their ability to further improve outcome following birth asphyxia. Most are already licensed for use in children and are close to the point for further evaluation within randomised controlled trials in babies who receive therapeutic hypothermia as part of their routine management.

ERYTHROPOIETIN

This naturally occurring glycoprotein is well known for its effect in stimulating erythropoiesis in the human neonate and is indeed used in a therapeutic setting to avoid neonatal anaemia.6 It has been shown that recombinant human erythropoietin (EPO) reduces the need for blood transfusions in very low birth weight babies when given after birth.

There is good evidence that EPO, a large molecule, crosses the blood brain-barrier by an active transport mechanism,6 although penetration may also occur as a result of damage to the blood brain-barrier following an hypoxic-ischaemic insult. In addition, EPO is expressed in astrocytes as a result of hypoxia and EPO receptors are abundantly present on brain capillaries. Intracerebral production of EPO in response to hypoxic stress has been reported in the neonate.7 EPO appears to have multiple neuroprotective properties including anti-apoptotic action probably mediated through reduction in caspase-3 activity. It has also been reported to inhibit intracerebral cellular inflammatory response although this response may be secondary to a reduction in the severity of neuronal necrosis. EPO has also been shown to ameliorate glutamate induced injury which leads to increased intraneuronal calcium concentration.

More recently EPO has been shown to have important neuroprotective effects in animal models and possibly in human neonates. In a recent review of the neuroprotective effects of EPO in neonatal animals (rat or mice),8 treatment given either before or after the cerebral insult improved short-term outcome in either histological studies with a reduction in neuronal injury or in a few studies where the animal was not killed and were later shown to have less functional impairment than control animals treated without EPO. In one study, 10-day-old rat pups given intraparenchymal EPO immediately after middle cerebral artery occlusion showed less asymmetrical limb movement in treated animals at 24 days after birth when compared to the vehicle treated controls.9 There is some suggestion that this effect is gender sensitive with females more sensitive than males.8 EPO depleted of sialic acid (asialo EPO) has no erythropoietic effect but enters the brain and triggers neuroprotective signalling mechanisms. It is rapidly cleared following intravenous administration.10 Asialo EPO has also been shown to be neuroprotective in a neonatal animal model.10,11

Studies of the neuroprotective effect of EPO in children and infants have shown promising preliminary results. Bierer et al12 followed up a group of infants with birthweight <1 kg who had been randomly allocated to either EPO supplementation (400 U/kg three times a week) or placebo, and found that those treated with EPO, particularly those with high neonatal plasma EPO levels, had a better neurodevelopmental outcome than a similar cohort with low serum levels.

Recently, the results of a randomised trial of term infants with moderate or severe hypoxic ischemic encephalopathy who were treated with EPO (300 or 500 U/kg) showed that infants who received EPO after birth have a significantly improved primary outcome (death or disability rate) than infants in the control group at 18 months after birth, but there were no differences in mortality alone between the two groups.13 The definition of moderate/severe disability included cerebral palsy, severe hearing loss, blindness or gross motor dysfunction (MDI <70). Surprisingly the time of the first recombinant human EPO dose was 1–48 h (median 20) after birth and thereafter every other day for 2 weeks. This suggests that EPO may provide neuroprotection over a longer period than the first 6 h after the asphyxial insult, but these results need to be confirmed by others.

MELATONIN

Melatonin is a naturally occurring hormone secreted by the pineal gland and mediates circadian rhythms. It is widely used in paediatric sleep disorders particularly in children with development problems. It acts as an antioxidant scavenging hydroxyl radicals and may stimulate other antioxidative enzymes such as superoxide dismutase. It has also been shown to reduce the inflammatory response of microglia. An anti-apoptotic effect may occur either directly or indirectly through these mechanisms. It readily crosses the blood-brain barrier and has been evaluated for its neuroprotective effects. Melatonin has been evaluated in adults with focal stroke lesion and has been shown to improve outcome in varying dosage range, but maximum efficacy was found when dosages exceeding 5 mg/kg were given within 60 min of the onset of the stroke.14
Studies in immature animals have shown an impressive neuroprotective effect when given both before and after hypoxic-ischaemic insult although this is probably dose-dependent. Experiments in term fetal sheep did not show an effect\(^1\) when a small dose (1 mg/kg) was used. In rat and mice pups melatonin administration in a dosage range 5–15 mg/kg\(^{16-19}\) showed reduced neurotoxicity following experimental asphyxia lesions although this effect appeared to have predominant benefit to the developing white matter rather than cortical tissues.\(^{16,17}\) It has also been shown to protect against functional damage in surviving animals.\(^{17}\) Melatonin given to immature animals appears to have effects in both reducing microglial activation as well as reducing free radical load.

The role of melatonin in human infants has also been evaluated in two studies. In a study of 20 septic infants and 10 controls, melatonin (two doses orally of 10 mg separated by a 1 h interval) showed no adverse effect but there was a reduction in inflammatory markers in treated babies.\(^{20}\) This same research group administered melatonin (10 mg intravenously) in multiple doses (total 80 mg) to 10 asphyxiated term infants and compared them with 10 equally asphyxiated babies who did not receive melatonin.\(^{21}\) The treated babies showed a significant reduction in products of lipid peroxidation up to 24 h after treatment. There were no adverse effects in the treated group with no deaths, but three of the control babies died.

In summary, melatonin is already widely used in pediatrics and has been given to sick neonates without apparent harm. Perinatal animal experiments suggest that it has powerful effects which may reduce neurotoxicity but the evidence to date suggests that white matter is more susceptible to protection than grey matter. Dosage as low as 5 mg/kg appear to be neuroprotective. Consequently clinical trials of melatonin may be more effective in premature babies vulnerable to periventricular leukomalacia than term asphyxiated infants.

**MAGNESIUM SULPHATE**

Magnesium is a naturally occurring ion in both the intracellular and extracellular spaces. Hypomagnesaemia is readily treatable by infusion of magnesium sulphate (MgSO\(_4\)) solution and this has been used for many years and in appropriate dosage is a safe substance licensed for use in the newborn.

Magnesium acts as a natural antagonist at N-methyl-D-aspartate (NMDA) glutamate voltage-dependent channels with evidence that it reduces excessive intracellular Ca\(^{2+}\) entry following glutamate stimulation as occurs as a result of asphyxial injury.\(^{22}\) Mg\(^{2+}\) may also have direct actions on mitochondrial activity and MgSO\(_4\) has been shown to have anti-convulsant properties.\(^{24}\) These actions are potentially neuroprotective.

There is good evidence that MgSO\(_4\) is neuroprotective in mature rat pups when given after experimental focal stroke lesions\(^{23}\) with a dose-response effect in that the higher dose is more neuroprotective.\(^{25}\) Other studies have shown that the neuroprotective effect of MgSO\(_4\) infusion is maintained when the infusion starts either at 2 or 4 h after recovery from the experimental stroke lesion but not when given 6 h after the event.\(^{26}\) More recently Knuckley’s group has reported a minimal beneficial effect for magnesium treatment unless hypothermia was included into the post infarction management regimen.\(^{26,27}\) Although hypothermia on its own was associated with mild neuroprotection there was an impressive and statistically significant additive effect in reduction of the total infarct volume when MgSO\(_4\) infusion was given together with mild hypothermia (35°C) in adult rats.\(^{26}\)

Considerable interest in the neuroprotective effects of MgSO\(_4\) on the vulnerable preterm fetus has resulted in a number of randomised control trials which report an improvement in neurological outcome with reduction in rates of cerebral palsy.\(^{28-30}\) The largest study published to date\(^{30}\) enrolled 2241 pregnant women at imminent risk of delivery between 24 and 31 weeks of gestation who were given an infusion of MgSO\(_4\) or placebo solution. Follow-up of over 95% of surviving infants showed that the rate of primary outcome (death or moderate/severe cerebral palsy) was not significantly different between the two groups, but there was a significantly reduced rate of cerebral palsy in surviving infants (a prespecified secondary outcome) in the MgSO\(_4\) group (RR 0.55; CI 0.52 to 0.95).

Recently a group in India treated 40 term asphyxiated infants with MgSO\(_4\) (3 doses of 250 mg/kg/dose) or placebo.\(^{31}\) Outcome was reported at discharge from hospital and the MgSO\(_4\) treated group had an overall better composite assessment of short-term outcome than the placebo group (OR 5.5, CI 1.2 to 23.6). There were two deaths in each group. Twenty-two per cent of the survivors in the treatment group had neurological abnormalities at discharge compared with 56% in the placebo group (OR 0.22, CI 0.05 to 0.90). No complications of the treatment were noted.

In summary, MgSO\(_4\) is a routinely used substance in perinatal clinical practice and in standard dose appears to be safe although higher doses may be associated with hypotension.\(^{32}\) It appears to be neuroprotective in animal and human studies, although its effects are most beneficial when used shortly after the asphyxial event. Neuroprotective effects have been shown in both human fetuses and newborns but further studies need to be performed. There is an intriguing suggestion from an animal focal stroke model that there is an additive benefit when MgSO\(_4\) is used in combination with mild hypothermia.

**TOPIRAMATE**

Topiramate is widely used as an antiepileptic drug in paediatric patients and it has several mechanisms of action. It modulates inhibitory gamma-aminobutyric acid (GABA)-mediated neuroreceptors and blocks presynaptic AMPA excitatory channels. GABA has predominantly neuroinhibitory effects in the mature central nervous system but in the immature brain appears to act as an excitatory neurotransmitter. Therefore inhibition of GABA-sensitive excitatory synapses may be particularly useful mode of action in protecting the immature brain.

Animal studies have shown a beneficial effect of topiramate in protecting the brain following both focal\(^{33}\) and global asphyxial\(^{34}\) insult. Topiramate suppresses acute seizures in a neonatal asphyxiated rat pup (P10) model and reduced neurological fragmentation.\(^{35}\) Furthermore, it was shown that topiramate also improves cognitive ability in a group of perinatally asphyxiated rat pups treated with this drug prior to a second insult (status epilepticus) compared with non-treated animals.\(^{36}\) In a study of newborn piglets topiramate showed a dose-related neuroprotective effect after a severe global hypoxic-ischaemic insult.\(^{34}\) The higher dose (20 mg/kg) was more effective than a lower dose (10 mg/kg) when given 1 h after the global insult.\(^{34}\) The higher dose showed a marked reduction in the severity of neuronal injury compared with a placebo group and even the lower topiramate dose group. As there was no significant reduction in the number of seizures in any of the three groups the neuroprotective effect was thought unlikely to be mediated through topiramate’s antiepileptic action.
A second study in immature rat pups did not show a neuroprotective effect of topiramate (50 mg/kg) alone, but very significant neuroprotection was achieved when hypothermia was added to the post-insult topiramate regimen. Hypothermia and topiramate was more neuroprotective than hypothermia without topiramate. This effect persisted at 4 weeks after the insult as the animals exposed to both topiramate and hypothermia showed less functional neurological impairment than the untreated group.

Topiramate appears to be a well tolerated and effective antiepileptic drug in children in recommended dosage of up to 7.5 mg/kg. There is as yet no intravenous preparation widely available in the UK, but nevertheless topiramate appears to be a candidate neuroprotective agent together with hypothermia for evaluation in a randomized control trial in asphyxiated babies.

**XENON**

Xenon (Xe) has been widely used in an isotopic form for measurement of cerebral blood flow in neonates. It is a rare noble gas that is used in anaesthesia and has a remarkably low toxicity profile. It is a very expensive gaseous agent and must be scavenged and reused in an anaesthetic circuit in view of its cost.

Xe has been shown to have neuroprotective properties in both cell culture and perinatal animal studies. It is a potent inhibitor of NMDA receptor channels, but has no effect on GABA receptor channels. It has been suggested that the neuroprotective effect of Xe must involve other mechanisms as well as its NMDA effects as the benefit seen in animal studies cannot be accounted for solely by this effect. Other effects may include presynaptic activity, and inhibition of other glutamate receptor channels.

Studies largely from Thoresen’s group in Bristol have reported very promising effects of Xe in conjunction with hypo-thermia in a 7-day-old rat pup model of global hypoxic-ischaemic insult. They showed that 50% Xe in a normothermic environment produced only a moderate reduction in histological brain damage as well as a improved functional outcome in surviving animals, but 50% Xe together with hypothermia had a much more impressive effect in reducing brain damage and improving functional outcome assessed when the adolescent rats were 10 weeks old. This study resulted in ~55% improvement with hypothermia alone compared with ~70% improvement when hypo-thermia was combined with 3 h of Xe. A second study showed that in animals subject to therapeutic hypothermia, 50% Xe gas exposure for 3 h resulted in better outcome than exposure for only 1 h. In addition the beneficial effect of 50% Xe was as great when delayed for 2 h after recovery from the insult as when given immediately after recovery. There were no differences in the pathology score when males were compared with females but longer-term studies on functional outcome showed that females did significantly better than males when tested at 8–11 weeks after the insult.

Xe is a very promising apparently safe and non-toxic neuroprotective agent which is additive in its effect to that of hypothermia. Its use in humans, however, will be limited by its cost and the necessity for an effective scavenging and rebreathing technique coupled to a ventilator which will confine its availability to a relatively few specialist centres.

**CONCLUSIONS**

Therapeutic hypothermia for term human infants has fundamentally improved outcome for what had previously been a very depressing condition with no effective management. This shows that neuroprotection following a severe hypoxic-ischaemic insult is possible and increases the chances of achieving a further incremental improvement by other techniques. This article has reviewed those drugs which are currently available for evaluation and can be potentially assessed as part of new randomised control trials of hypothermia plus additional therapy. The great success of the TOBY study in Britain and Europe shows that there is enthusiasm for enrolling babies in such randomised controlled trials and the organisers of the TOBY trial are enthusiastic to plan a ‘TOBY-Plus’ study based on one or more of these candidate drugs.

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