

DEXAMETHASONE (Commentary)

Choice of steroid for antenatal and neonatal use

Concerns exist over **antenatal** dexamethasone use, as outlined in the monograph on betamethasone and the associated web commentary, and there are suggestions that a preservative currently added to several widely-used parenteral preparations may be toxic to the developing brain. A paper published by Baud *et al.* in 2001 certainly provides convincing evidence that sulphites can damage the developing mouse brain, even in the low concentrations present in Soludecadron,[®] the product normally used in France (0.15 mg of sulphites/mg of dexamethasone). The formulations of Decadron[®] marketed by Merck, Sharpe and Dohme in much of Europe and North America also contain 1 mg/ml of this excipient, but some non-proprietary products are free of this preservative. Some clinicians believe that staff should probably avoid products with this excipient if they can when giving dexamethasone to a small baby both before and after birth.

Dexamethasone was the steroid used in almost all the early trials of **postnatal** use but interest has grown in the last five years into the use of hydrocortisone rather than dexamethasone, not only to control early hypotension, but also to reduce the incidence of bronchopulmonary dysplasia – a strategy triggered, in part, by a recognition that some of these babies seem to show evidence of poor adrenal gland reactivity at birth (Watterberg, *et al.*, 1995, 1999; 2004 and 2007). However, in the only trials done to date, while treatment had did not seem to be associated with any adverse long term effects (or any adverse short term effects either other than an increased risk of intestinal perforation), hydrocortisone did not deliver any statistically convincing short term benefits either (Halliday *et al.* 2009).

There have also been some suggestions that betamethasone may be as effective as dexamethasone (DeCastro *et al.*, 2009) and cause fewer immediately recognisable side effects. Whether there are fewer long term adverse effects has not yet been explored. Similarly there has been one study of the use of oral prednisolone to wean preterm babies who are still in supplemental oxygen at 36 weeks postmenstrual age from needing further oxygen supplementation (Bhandari *et al.*, 2008)

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Use of dexamethasone to minimise postnatal lung damage

Attitudes towards the neonatal use of systemic dexamethasone changed dramatically between 1999 and 2001. By 1999 a quarter of all very low birth weight (<1.5 kg) babies were being given high dose systemic treatment in many units either to prevent, or to treat, the chronic lung damage ('bronchopulmonary dysplasia' or BPD) caused by sustained ventilator support. A series of systematic reviews (including three authoritative reviews from the Cochrane Collaboration) had shown that systemic treatment did not seem to improve survival, but did speed weaning from respiratory support. Then, in late 1999, 14 years after this form of treatment was first reported, and 10 years after the first large trial was published, came news that trials of early prophylactic use were showing an excess of cerebral palsy among survivors. Many earlier studies had, unfortunately, satisfied themselves with short-term surrogate markers of success (Ehrenkranz & Mercurio, 1992). In addition, the one large early trial with good follow up information (Jones *et al.*, 1995) had probably offered false reassurance, since 40% of the control infants had also received 'open label' steroid treatment. Further large studies of early high dose treatment were also revealing numerous short-term side effects.

The American Academy of Pediatrics and the Canadian Paediatric Society issued a joint statement in April 2001. This listed evidence showing that early 'prophylactic' steroids carried an unacceptable risk when given

systemically, and that it did not work when inhaled. Then, towards the end of the year, the Committee on Safety of Medicines in the UK also put out “a warning about the possible association between dexamethasone and cerebral palsy.” Their recommendation about neonatal use was that “an assessment of risk/benefit should be made on an individual patient basis”. Everything that has happened in the four years since then has merely confirmed the magnitude of the mistake that clinicians (and research funding agencies) made in the early 1990s.

Early postnatal use: A further report on the long term outcome of the controlled trial of early postnatal dexamethasone use undertaken in Taiwan between 1992 and 1995 appeared in the *New England Journal of Medicine* in March 2004. This seems to have confirmed, in almost every particular, all the predictions made by those who first conducted a meta-analysis of the earlier fragmented follow up information. Dr Yeh and his colleagues studied 262 babies weighing less than 1 kg at birth over a three year period, and they managed to trace and see 92% of all the long term survivors 7–10 years later. Those given ‘prophylactic’ dexamethasone shortly after birth had poorer performance skills and a lower IQ (78.2 ± 15.0 v. 84.4 ± 12.6). They also had more disability (39% v. 22%). It clear, in retrospect, that early postnatal use of dexamethasone should never have come into indiscriminate widespread use before any controlled trials had looked at long term as well as short term outcomes.

Use 1–2 weeks after birth: The position when steroids are started ‘therapeutically’ 1–2 weeks after birth is less clear cut. The joint AAP/CPS statement summarised such information as was known in April 2001, and the table printed here summarises what had become known by the time Lex Doyle came to give his presentation at the ‘Hot Topics’ meeting in Washington in December 2001. There was a marginal, but non significant improvement in survival, and a marginal (nonsignificant) increase in cerebral palsy. It has, however, since been shown (Doyle *et al.*, 2005) that the risk of death or cerebral palsy is however lowest where the risk of chronic lung disease is highest. Low dose treatment, as in the DART trial protocol, greatly speeds extubation however, so there remains a strong case for reactivating this trial in babies at high risk of developing life-threatening chronic lung disease.

Outcome	Dexamethasone	Control	Event rate difference	
Survival	78.7% (199/253)	76.7% (184/240)	-0.03	-0.10 to 0.05
Cerebral palsy	21.9% (41/187)	15.6% (28/180)	0.06	-0.02 to 0.13
Major disability	25.9% (43/166)	20.8% (33/159)	0.03	-0.06 to 0.12
Survival without disability	60.0% (135/225)	60.8% (130/214)	0.01	-0.08 to 0.10

Conclusions: These findings have certainly re-energised the search for ways to avoid lung damage in the first place. Several small studies have shown that early constant positive airway pressure (nasal CPAP), with or without early surfactant treatment, can often make prolonged endotracheal intubation unnecessary. The Melbourne COIN Trial started to address these issues and the NICHD is currently conducting a rather similar trial (the SUPPORT trial) in America (Neil Finer: nfiner@ucsd.edu). The one strategy that does seem to significantly reduce the risk of chronic lung damage is the use of caffeine to speed early extubation (Schmidt *et al.*, 2008). How it delivers this benefit is however far from clear at the moment. The search for other approaches that cause less damage continues, but these will probably require a more objective definition of what constitutes a ‘need’ for supplemental oxygen at 36 weeks gestation (Ellesbury *et al.*, 2002; Walshe *et al.*, 2004). The current European CURPAP trial is, for example, testing whether elective brief intubation simply to give surfactant improves outcome in babies initially managed using CPAP.

However that does not solve the problem of what to do when severe lung damage does appear. No alternative strategy to steroid treatment has yet been identified, and most studies to date probably used higher doses than they needed to (Durand *et al.*, 2002). ‘Pulsatile’ treatment (Brozanski *et al.*, 1995) has still not been fully evaluated. It is also possible that a toxic preservative may account for some of the adverse outcomes seen in earlier trials (see above). Shamefully, the Australian DART trial, which had hoped to clarify some of these issues, closed in Oct 2002. It had only recruited 70 babies over three years, a tenth of the number it had known would be needed to provide a definitive answer to some of these questions (Doyle *et al.*, 2006). We are left little wiser than we were when anecdotal reports of the efficacy of dexamethasone for BPD first started to surface twenty years ago (Schick & Goetzman, 1983). The conclusion of yet another meta-analysis is that we still remain in urgent need of the sort of study of high versus low dose treatment that the DART trial tried to do, but failed to do for lack of support (Onland *et al.*, 2008).

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Use to facilitate extubation and minimize post-extubation stridor

A recent systematic review based on the outcome of five clinical trials involving 1873 adults who had had an endotracheal tube in place for at least 24 hours before extubation was attempted (Markovitz *et al.*, 2008) concluded that corticosteroids had *not*, as yet, been shown to significantly reduce in incidence of extubation failure. However, a further systematic review, which focused simply on those who needed reintubation because of stridor and presumed laryngeal oedema and excluded cases where reintubation was deemed necessary for other reasons, and which also included data from one more trial involving a further 80 adults, came to a very different conclusion a few months later (Fan *et al.*, 2008). While the assessed reduction in the need for reintubation computed during the second systematic review (a fixed Odds Ratio of 0.29 [95%CI 0.15 to 0.58]) may be overoptimistic because of publication bias, and the failure of many of the studies to report the outcome of any 'intention to treat' analysis, the results do seem to parallel those seen during a number of neonatal studies (cf. Doyle *et al.*, 2006). Benefit was,

however, only seen in these adult trials when 2–4 doses were given in the 12–24 hours before extubation was attempted (involving typically, in total, the equivalent of 20 mg of dexamethasone).

These findings do call for cautious interpretation however. In the adult trials included in this systematic review it looked as though somewhere between 10 and 50 adults had to be treated to stop one patient from requiring reintubation because of laryngeal oedema. If even a short course of steroid treatment can be harmful (as the CRASH trial involving use in patients with head injury seems to suggest) then it becomes important to limit prophylactic use to the minority of babies at really high risk of extubation failure. Identifying such a group is not going to be easy – babies who have already failed extubation once, not because of a lack of respiratory drive, but because of perceived upper airway obstruction and/or stridor, would seem to be the most obvious group to target for such treatment (Greenough and Prendergast, 2008).

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Steroid use to reduce chronic oxygen dependency in the very preterm baby

One non-randomised trial has suggested that giving a short course of prednisolone to very preterm babies who are still thought to be oxygen dependent when they reach a postmenstrual age of 36 weeks can help to wean a substantial number from the need for any further supplemental oxygen (Bhandari *et al.*, 2008). The dose regimen used in this study was 2 mg/kg of prednisolone by mouth twice a day for 5 days and then 1 mg/kg once a day on days 6, 7, 8, 10, 12, and 14. Views will vary as to how much effort should be put into trying to wean these babies from oxygen when they are in most respects almost ready for discharge home, and many will say that the first need will be to replicate this study as part of a formal double-blind randomised trial using an objective measure of oxygen “need” (Walsh *et al.*, 2004; Quine *et al.*, 2006) and sustained follow up to confirm that there are no adverse long term effects to set against the short term benefits.

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Steroid use to control neonatal hypotension

Dexamethasone has been used with increasing frequency to control neonatal hypotension in the last ten years (as has hydrocortisone), and a study appeared several years ago showing that mortality among such children, and morbidity among the survivors one year later, is very much higher than it is in those not so treated (Finer *et al.*, 2006). It is, of course, more than likely that the poor outcome is simply a consequence of the hypotension, or of the underlying illness that caused the hypotension, and not of the treatment used to combat that hypotension. It is, however, an assumption and, given the time it took to realise that the pre-emptive use of dexamethasone to minimise the risk of lung damage was sometimes doing more harm than good, it would be a courageous clinician who denied that need for a properly conducted controlled trial to clarify these issues. Does pressure matter, or is it flow (and the delivery of oxygen to the tissues) that really matters? Does the drop in pressure cause damage, or is this simply a response to damage that has already occurred? And what is the minimum safe and effective dose? Another relatively recent paper (Ng *et al.*, 2006) suggests that low dose treatment is much more effective than is generally realised. Use seems particularly hazardous in babies also being given indometacin (q.v.).

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Steroid use in croup

Croup (the sudden onset of hoarseness, a barking cough, and distressing inspiratory stridor) is common in young children. It is mainly viral in origin, though atopy plays a part in some children. Symptoms often settle almost as fast as they arise. Humidification, and oro-nasal decongestants are often used, although there is little objective evidence that they are of any real benefit. Antibiotic treatment is not indicated, but oxygen should clearly be given if there is evidence of hypoxaemia. Brief steroid use can reduce admission and readmission, and only 1% of those admitted require intubation (once cases of bacterial epiglottitis are recognized for what they are). Giving two 1 mg doses of nebulised budesonide (q.v.) 30 minutes apart can reduce the need for hospital admission, but a single 0.6 mg/kg oral (or IM) dose of dexamethasone is just as effective and easier to administer (because nebulisation can take 15 minutes and frequently triggers prolonged agitation and crying). Dexamethasone seems to be more effective than an equivalent dose of prednisolone, presumably because of the longer half life (36–72 hours rather than 12–36 hours). The systematic review of glucocorticoid use in croup undertaken by Russell *et al.* in 2004 identified more than 30 randomised controlled trials involving more than 3,700 babies, some of which had been undertaken more than 40 years ago. Many studies seem to have been done by clinicians who did not realize how much evidence of efficacy already existed.

Geelhoed GC, Klassen TP, Williamson J, *et al.* Efficacy of a small single dose of oral dexamethasone for outpatient croup: a double blind placebo controlled trial. *BMJ* 1996;**313**:140–2. [RCT]

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Russel K, Wiebe N, Saenz A, *et al.* Glucocorticoids for croup. *Cochrane Database Syst Rev* 2004;(1):CD001955.

Sparrow A, Geelhoed G. Prednisolone versus dexamethasone in croup: a randomized equivalence trial. *Arch Dis Child* 2006;**91**:580–3. [RCT]

Steroid use in meningitis and septic shock

Meningitis: Dexamethasone, started early, can modify the long term outcome in children with bacterial meningitis, as the trial by Lebel *et al.* first established in 1988, and as the current *Formulary* monograph stresses. Nevertheless, until recently, the only clear evidence of benefit came from children with meningitis due to *Haemophilus influenzae* (an infection now rarely seen in those countries where almost all children are offered the Hib vaccine within months of birth). In addition, the only trial outcome of unequivocal statistical significance was a decrease in the number of survivors developing serious deafness. The report of a large trial in Malawi involving 598 children cast further doubt on the utility of such a strategy (Molyneux *et al.*, 2002), but it has to be remembered that many of the children in the African trial were quite ill by the time they were first seen for treatment.

A recent Cochrane review of all the trials involving children and adults reported a marginally significant decrease in the number of deaths (relative risk (RR) 0.76; 95% confidence intervals (CI) 0.59 to 0.98), and a very significant reduction in the risk of severe deafness in survivors (RR 0.36; 95% CI 0.22 to 0.60). Most of the 1853 patients in these 18 trials were children. However, this review was issued before the trial from Malawi was published, and shortly before a further European trial was published (de Gans *et al.* 2002). In that study, involving 301 adults with early bacterial meningitis, immediate treatment with dexamethasone was associated with a significant reduction in mortality (RR 0.48; 95% CI 0.24 to 0.96; *P* = 0.04). The trial only established clear evidence of benefit in the 108 patients who had pneumococcal (*Streptococcus pneumoniae*) infection. There was no evidence of benefit in the 97 with meningococcal (*Neisseria meningitidis*) meningitis, but the authors concluded that their findings could be used to justify steroid use in any patient with bacterial meningitis. Tunkel and Scheld, in their commentary, were more cautious, and suggested that steroids should only be given to those with pneumococcal meningitis because that was the only group where treatment seemed to be of benefit.

Failure to demonstrate benefit is not, of course, the same thing as saying that benefit does not exist. It took four years to complete the African trial and nine years to complete the European trial, so we are not going to have further evidence on this issue for some time. Nevertheless, it can, at the very least, be said that there is no evidence that treatment was harmful to those with meningitis due to other bacterial organisms in the European trial (or any evidence that treatment was harmful in the African trial). Given

that treatment usually needs to be started before the causal organism is known, this is important information.

We now have evidence, therefore, that the **early** treatment of at least some forms of bacterial meningitis – initiated before, or with, the first dose of an antibiotic – can reduce the risk of death, and the risk of survival with a severe disability both in children and in adults. We do not know if this is true for all organisms, and we do not know if it is true in the first month of life. However, we do know that neonatal bacterial meningitis remains a devastating illness (Heath, *et al.*, 2003), and that a fifth of the survivors have at least some residual disability ten years later (Stephens, *et al.*, 2003). What is more, many of these infections arise while the child is still in hospital, which should maximise the chance of treatment being started promptly.

One early non-randomised study (Yu and Grauaug, 1963) suggested that dexamethasone could improve outcome, but a more recent controlled trial in Jordan (Daoud *et al.*, 1999) concluded that steroid treatment ‘does not improve the outcome of neonatal bacterial meningitis’. In this study, which involved 52 full term babies, 22% of treated and 28% of control babies died, while 30% of the treated and 39% of the control survivors had some disability at 2 years. The outcome of a collaborative trial in North America, started by Professor McCracken, was never published because follow up information was inadequate. In summary, there is no evidence that a short course of dexamethasone does any harm, and a very real risk that a valuable treatment strategy could be being ignored because the only neonatal trial undertaken to date was under-powered to detect a modest but valuable beneficial effect. Many would argue that a treatment of known benefit to children and adults should not be dismissed as of no benefit in the first month of life merely because no trial of adequate size has yet been mounted.

A recently completed controlled trial has shown that dexamethasone can also improve survival in adults with tuberculous meningitis (Thwaites *et al.*, 2004) although it does not seem to reduce the number surviving with severe disability. Whether such a strategy would work in children has never been formally tested. TB meningitis is such a devastating condition that treatment often needs to be started on the basis of a presumptive diagnosis before formal laboratory confirmation is available. Many in southern Africa currently give all such children 2–4 mg/kg of dexamethasone once a day for the first month of treatment in the belief that the inflammatory response and, more particularly, the vasculitis seen in this condition is a hypersensitivity reaction.

Septic shock: The recent CORTICUS trial in adults found that a 50 mg dose of hydrocortisone every 6 hours for 5 days did nothing to improve survival in adult patients with septic shock (Sprung *et al.*, 2008).

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How long does high-dose steroid treatment depress adrenal function?

High dose corticosteroid treatment depresses adrenal function and the response of the adrenal gland to stress in the very preterm baby in just the same way as it does in later life. Pituitary function would seem to recover rather faster than either the hypothalamus or the adrenal gland. Treatment for one week causes clear depression, and this is even more marked after three weeks of treatment, but substantial recovery can usually be seen four weeks after treatment ends, but serum cortisol levels had still not returned to normal after one month.

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Should low cortisol levels be corrected ?

Several studies have reported that low basal cortisol levels and/or lower responses to corticotropin are commonly seen in babies who later develop BPD, but a large randomized trial of the prophylactic treatment of very low birth weight babies with physiologic replacement doses of hydrocortisone in the first two weeks of life did not reduce mortality or the incidence of BPD, although it did seem to have some impact in a sub-group with chorioamnionitis (Watterberg *et al.*, 2004). What further work by the PROPHET Study Group has now shown is that while low cortisol concentrations are not predictive of adverse short-term outcomes, high cortisol levels are associated with severe intraventricular haemorrhage, and extremely high levels were associated with morbidity and death (Aucott *et al.*, 2008). The most plausible interpretation of these findings is, of course, that these high values are a response to the stress that triggered the intracerebral bleed, or the stress caused by the bleed, and not the *cause* of the bleed or the adverse outcomes.

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