

PERSONAL PRACTICE

The effectiveness and side effects of dexamethasone in preterm infants with bronchopulmonary dysplasia

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The incidence of bronchopulmonary dysplasia (BPD) among ventilated infants is estimated to be between 4 and 40% depending on gestation but undoubtedly the highest incidence, in excess of 70%, occurs in infants weighing 1000 g or less at birth.¹ The incidence of BPD may further increase in the coming decade as advances in neonatal intensive care enable clinicians to save even smaller, lower gestation, and more critically ill infants. BPD is already a major cause of mortality and long term morbidity. A significant proportion of infants will be oxygen dependent for a prolonged period of time. Growth delay and neurodevelopmental deficit have also been reported with increasing frequency.¹ Thus, effective therapeutic measures are urgently required.

Dexamethasone, a potent, long acting steroid with almost exclusive glucocorticoid property, was intensively studied and appeared promising in improving pulmonary function. This article examines the efficacy and adverse effects of dexamethasone treatment in preterm infants with BPD.

Mechanism of action

Several modes of action have been proposed to explain the association between steroid treatment and improvement in lung function. They include an increase in surfactant synthesis^{2 3}; enhancement of β -adrenergic activity⁴; stimulation of antioxidant production²; stabilisation of cell and lysosomal membrane⁵; breakdown of granulocyte aggregates with improvement in the pulmonary microcirculation^{6 7}; inhibition of prostaglandin and leukotriene synthesis^{8 9}; removal of excess lung water¹⁰; and suppression of the cytokine mediated inflammatory reaction in the lung.¹¹ The latter two theories are of particular interest and may provide an explanation for the rapid changes in lung function.

Ariagno *et al* demonstrated a marked steroid induced reduction in lung water content in newborn mice raised in an 80% oxygen environment.¹⁰ They showed that the decrease in lung water was due to a loss of fluid from the interstitial tissue of the lung with no reduction in the thickness of the blood-gas barrier. Sahebji *et al* have also shown that steroids can accelerate the resolution of pulmonary oedema and improve alveolar volume

either by increasing the rate of reabsorption or decreasing the formation of alveolar fluid exudate.¹² Further support for the lung fluid theory comes from a recent study that demonstrated that diuresis occurred within 48 hours of the commencement of dexamethasone in preterm infants with BPD.¹³ This diuretic phase correlated closely with the period of improved lung function.

Another plausible explanation may relate to the ability of corticosteroids to suppress the inflammatory process induced by barotrauma and oxygen toxicity. The cytokine, tumour necrosis factor- α (TNF- α), was not present in the bronchopulmonary secretions of ventilated preterm infants until after four days of postnatal age.¹¹ Thereafter, the concentration increased progressively and the highest concentrations were found in babies with BPD who required prolonged ventilatory and oxygen support. It was of interest to note that the time course of TNF- α production correlated well with the pattern of inflammatory cell migration into the lungs. The influx of polymorphonuclear neutrophils and activated alveolar macrophages in turn triggered an inflammatory reaction leading to pulmonary fibrosis.¹⁴ The concentrations of TNF- α and inflammatory cells from bronchopulmonary lavage were dramatically decreased within 24 hours of starting steroid treatment.¹¹ Dexamethasone decreased the synthesis of the cytokine and limited the polymorphonuclear cell and macrophage migration to the inflamed area. Hence, it has the ability to restrain the alveolar macrophage induced alveolitis and prevent the full activation of the inflammatory cascade.

Despite intensive research, the exact mechanism to explain the action of dexamethasone has not been fully delineated. As the pathogenesis of BPD is complex and multifactorial, it is likely that more than one mechanism is responsible for the acute and rapid improvement of pulmonary function seen with steroid. The overall picture appears to be that dexamethasone probably exerts its effect by reducing the tracheo-bronchial alveolar inflammatory response and pulmonary oedema, thereby facilitating gas exchange, airway patency, and improving lung compliance which enables successful extubation.

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Table 1 Use of steroids in BPD: prospective/controlled studies

Authors	Study design	No of patients	Results	Complications
Mammel <i>et al</i> (1983) ¹⁵	Prospective, double blind, randomised, placebo controlled, crossover, sequential analysis	6	↓ Alveolar-arterial oxygen gradient ↓ Peak inspiratory pressure ↓ Fractional inspiratory oxygen ↓ Ventilatory rate ↑ Weaning from respirator	Major problems with sepsis (subacute bacterial endocarditis, septicaemia, cytomegalovirus infection, pneumonia)
Avery <i>et al</i> (1985) ¹⁶	Prospective, double blind, randomised, placebo controlled, sequential analysis	14 (7 treated, 7 controls)	↑ Dynamic pulmonary compliance ↑ Weaning from respirator	Hypertension, hyperglycaemia, sepsis, longer duration of hospitalisation in treated infants
Ariagno <i>et al</i> (1987) ¹⁷	Prospective, double blind, randomised, placebo controlled	21 (10 treated, 11 controls)	↑ Total respiratory system compliance ↑ Weaning from respirator	Hypertension, hyperglycaemia, Gram negative sepsis, gastrointestinal haemorrhage
Cummings <i>et al</i> (1989) ¹⁸	Prospective, double blind, randomised, placebo controlled	36 (13 treated on 42 days' course, 12 treated on 18 days' course, 11 controls)	Treated <i>v</i> control ↓ Mean airway pressure ↓ Ventilatory rate 42 days treated <i>v</i> 18 days treated and controls ↑ Weaning from respirator ↑ Weaning from supplemental oxygen Improve neuro-developmental outcome Tendency to ↓ duration of hospitalisation	Pulmonary airleaks, adrenocortical suppression
Harkavy <i>et al</i> (1989) ¹⁹	Prospective, double blind, randomised, placebo controlled	21 (9 treated, 12 controls)	↓ Oxygen requirement (in first 10 days of treatment) ↑ Weaning from respirator	Hyperglycaemia, delay in weight gain
Ohlsson <i>et al</i> (1989) ²⁰	Prospective, double blind, randomised, placebo controlled	23 (10 treated, 13 controls)	↑ Weaning from respirator	Hypertension, glucosuria, leukocytosis, bradycardia
Noble-Jamieson <i>et al</i> (1989) ²³	Prospective, double blind, randomised, placebo controlled (non-ventilator dependent infants)	18 (9 treated, 9 control)	↓ Oxygen requirement (1 week after steroid but did not shorten the time weaning to room air)	Leukocytosis, weight loss, periventricular echodensity (± cyst formation)
Kazzi <i>et al</i> (1990) ²¹	Prospective double blind, randomised, placebo, controlled (oral steroids)	23 (12 treated, 11 controls)	↓ Oxygen requirement (day 8 and 17 after initiation of treatment) ↑ Weaning from respirator	Hypertension, glucosuria
Singhal <i>et al</i> (1990) ²²	Prospective, double blind, randomised, placebo controlled	31 (12 treated, 19 controls)	No improvement in lung function	Hypertension
Collaborative Dexamethasone Trial Group (1991) ²⁴	Multicentre, prospective, double blind, randomised, placebo controlled	285 (94 treated ventilator dependent, 49 treated non-ventilator dependent, 94 controls ventilator dependent, 48 controls non-ventilator dependent)	↑ Weaning from respirator (tendency to ↓ duration of hospitalisation and ↓ duration of supplemental oxygen)	Hypertension, hyperglycaemia

Increase=↑, decrease=↓.

Efficacy

There are 10 published prospective, randomised, controlled trials concerning the use of dexamethasone in BPD. Eight were from North America and involved relatively small numbers of patients.¹⁵⁻²² Two were from the UK,^{23, 24} of which one was a large international multicentre study organised by the Collaborative Dexamethasone Trial Group in Oxford.²⁴ The findings of these trials are summarised in table 1.

There is now ample evidence to show that dexamethasone improves lung function and compliance in BPD infants within 72 hours of commencement^{16, 17} and in turn facilitates weaning from assisted ventilation and extubation.^{15-21, 24} However, with respect to the duration of supplement oxygen treatment and length of hospital stay, the impact of dexamethasone is less certain. Only one report demonstrated a significant decrease in the duration of supplemental oxygen requirement when a prolonged 42 day course was given.¹⁸ Although the collaborative trial group also

reported a favourable trend,²⁴ such a claim was not substantiated by other randomised trials. Two reports showed a positive trend in favour of a shorter duration of hospitalisation in the steroid treated group, but the difference was not statistically significant.^{18, 24}

Perhaps the most important claim for beneficial long term effects of steroids in BPD was made by Cummings *et al*, who showed a significant improvement in the neurodevelopmental outcome of 6 and 15 months in infants treated with a 42 day course of dexamethasone.¹⁸ As this is the only randomised study that provides data on neurodevelopmental outcome and involved only a small number of patients, a definite conclusion cannot be drawn as yet. A three year follow up assessment from the collaborative trial group will hopefully provide us with some answers in the near future.

None of the randomised trials performed to date have managed to show an improvement in the mortality rate of steroid treated infants compared with controls.¹⁵⁻²⁴

Treatment strategy

Unfortunately, there are no universally agreed guidelines on the most appropriate indication, timing, dosage, and regimen of dexamethasone to use as different clinical trials have their own experimental design and outcome measures. So far, only a general trend was emerged.

(1) INDICATIONS

Dexamethasone is only of proved value in infants who develop BPD and have difficulty in weaning from the ventilator.^{15-21 24} At present, there is not enough evidence to extend its recommendation to infants who are oxygen dependent but are not ventilated. Although in the latter group, a transient reduction in oxygen requirement has been demonstrated, the overall duration of oxygen dependency was not shortened.^{23 24}

Babies who show continuous and steady improvement or suffer a temporary setback in ventilation, especially due to sepsis, must not be hastily put on dexamethasone. It is also essential that every effort is taken to identify all treatable causes that may prevent successful weaning before any baby is commenced on steroid treatment. Factors like anaemia and metabolic derangements must be corrected; haemodynamically significant patent ductus arteriosus must be treated; sepsis should be excluded by C reactive protein and blood cultures; and plasma caffeine concentrations must be maintained well within the therapeutic range of facilitate diaphragmatic function and to prevent apnoea. Only after exclusion of all these treatable causes should dexamethasone be considered as the next option.

(2) TIMING

In most studies infants were started on steroid treatment between the second and fourth week of postnatal age.¹⁶⁻²² Dexamethasone given during that period is proved to be of value with regard to weaning from the ventilator. Interestingly, recent evidence suggests that dexamethasone given much earlier for the treatment of respiratory distress syndrome on day 1 is also effective in improving pulmonary status and facilitating extubation.²⁵ By minimising barotrauma and oxygen induced toxicity in the initial period, steroids are potentially able to reduce the incidence of lung injury. Furthermore, we have recently demonstrated that TNF- α in endotracheal aspirate only appears in significant quantity after day 4 of postnatal age¹¹ and perhaps this represents the most appropriate timing for starting steroid treatment to suppress pulmonary inflammation. Another advantage of starting dexamethasone treatment on day 4 is to allow the exclusion of congenital infection, which is at times impossible to differentiate from respiratory distress syndrome. A double blind randomised study is currently underway at our institution to investigate the effect of day 4 steroid on ventilation parameters and its impact on the incidence and severity of BPD.

(3) DOSAGE AND DURATION OF TREATMENT

The recommended starting dose of dexamethasone is in the region of 0.5-1 mg/kg/day, which is a relatively large dose to weight ratio.¹⁵⁻²⁵ As a lot of undesirable effects of corticosteroids are dose dependent, such as protein catabolism, adrenal axis suppression etc, using a lower starting dose will certainly be advantageous if it can produce the desired anti-inflammatory effect. Unfortunately, no trial has so far made any direct comparison of different dosages. At present, the only recommendation is to start dexamethasone treatment at about 0.5-0.6 mg/kg/day but almost certainly in future this dosage can be more finely tuned according to the severity of lung disease in individual babies.

Unlike the starting dose, the dose tapering schedule and duration of treatment differ substantially between different centres.¹⁵⁻²⁴ So far, only Cummings *et al* have studied the effectiveness of dexamethasone treatment in relation to the length of treatment.¹⁸ They concluded in their small cohort of patients that the prolonged 42 day course was superior to an 18 day course or placebo with respect to pulmonary and neurodevelopmental outcomes.

My experience with the use of dexamethasone in BPD indicated that prolonged dependency on the drug is not unusual. With a short 10 day course of treatment similar to the one used by the multicentre study,²⁴ a significant proportion of infants required to be reventilated after the cessation of the course of treatment and a second course is frequently needed at a later stage. Therefore we modified our course to a three week dose tapering regimen starting with an initial dose of 0.6 mg/kg/day for the first week, reducing to 0.3 mg/kg/day for the second week, and 0.15 mg/kg/day for the final week. The incidence of extubation using this three week course is comparable with longer courses,^{15 16 18} and our observation is also supported by studies that use a similar length of treatment.¹⁹⁻²¹

As few data have been published to indicate the most appropriate and effective regimen, I can only recommend a dose tapering treatment period of no less than three weeks in order to prevent relapse and with a view to extend the duration to six weeks if further studies are able to confirm the finding of Cummings *et al*. In principle, the most important rule governing the use of steroids is to use the minimum dose and the shortest duration of treatment possible to achieve the desired anti-inflammatory action.

(4) SECOND COURSE OF STEROID

To date, no scientific trial has focused on the use of a second course of dexamethasone in BPD. The following data is based on personal clinical experience and observation over a four year period, from 1987 to 1990. Sixty nine very low birthweight infants were commenced on dexamethasone. Seven (10%) died while on the first three week course of steroid. Of the 14 (20%) infants who received a second three week course of treatment, six were

ventilator dependent when the course started and eight were in headbox oxygen greater than 40%. In the ventilated group, dexamethasone was obviously given as a rescue measure after all forms of conventional treatment had failed. All six infants responded initially with a reduction in ventilation and oxygen requirement but only four continued to show adequate improvement to permit extubation. The other two infants continued to deteriorate and required increasing ventilatory support. They eventually died because of BPD and respiratory failure. As to the unventilated, oxygen dependent group, dexamethasone was given to minimise supplemental oxygen requirement. A transient beneficial effect was observed in the first week but in most cases oxygen requirement increased as the dose of steroid was reduced. All infants in this group survived.

As this is a clinical observation, and involves only a small number of infants, it does not allow a firm conclusion to be drawn with regard to the use of a repeat course of dexamethasone. However, a 67% success rate of extubation in the ventilated group is encouraging. I have no hesitation in trying a second course of steroid when an infant remains stuck on the ventilator while all other therapeutic options have already been attempted.

The adverse effects of dexamethasone

Although the side effects of corticosteroids have been extensively investigated in older children and adults, they have not been com-

prehensively and systematically examined in preterm infants. Most randomised trials have concentrated on the efficacy of the drug with the question of safety inadequately addressed. Despite the sporadic nature of reporting adverse effects, an impressively long list of complications has already been accumulated (table 2). Those highlighted by the asterisk represent the side effects of dexamethasone that have been reported in preterm infants.

(1) CENTRAL NERVOUS SYSTEM COMPLICATIONS

The most worrying complication is the recent animal studies concerning central nervous system developments when corticosteroids are used during the perinatal period. Experiments with newborn rodents indicate that corticosteroids can cause a substantial decrease in brain weight^{26 27} and cerebral and cerebellar DNA content.^{27 28} It can also cause delay in cortical dendritic branching,²⁶ and severely disrupt the process of postnatal glial cell formation.²⁷ These experiments clearly demonstrate that perinatal corticosteroid treatment is capable of exerting a permanent and irreversible effect on neural cell division and differentiation.

Despite many serious sequelae noted in fetal and newborn animal studies, there are relatively few data regarding the adverse effect of corticosteroids in human brain development. The effects of antenatal dexamethasone treatment on neurodevelopmental outcomes were assessed by the collaborative group on antenatal steroid treatment.²⁹ No detectable differences with regard to head circumference or neurodevelopmental abnormalities could be found at 9, 18, and 36 months that could be attributed to the effect of antenatal dexamethasone treatment. In fact, neurodevelopment was more strongly influenced by socio-economic background. Other investigators who used corticosteroid in the early postnatal period also found no difference with regard to neurodevelopmental outcome in the treated infants.^{30 31} One of the most recent reports suggested that an extended 42 day course of dexamethasone was superior to a shorter 18 day course or placebo in terms of neurodevelopmental outcome at 6 and 15 months.¹⁸ Published evidence on neurodevelopmental outcome in human newborn suggest that there is no major risk associated with the use of corticosteroid treatment in the neonatal period.

(2) OPHTHALMOLOGICAL COMPLICATIONS

In one animal study it was suggested that dexamethasone treatment might increase the risk of retinopathy of prematurity by causing rapid changes in oxygenation.³² Although two human studies support such claims,^{33 34} there are at least four other trials that failed to demonstrate an increase in the incidence or severity of this problem.^{18 19 21 31}

(3) CARDIOVASCULAR COMPLICATIONS

Hypertension secondary to sodium retention

Table 2 Complications of corticosteroid treatment

1. Central nervous system	Pseudotumour cerebri Gross motor developmental retardation* Abnormalities of electroencephalography* New ultrasonographically diagnosed echodensities*
2. Ophthalmological	Glaucoma Posterior subcapsular cataracts Reactivation of dormant herpes keratitis Exacerbation of fungal and bacterial eye infections Retinopathy of prematurity*
3. Cardiovascular	Hypertension* Cardiac hypertrophy* Sustained bradycardia*
4. Respiratory	Pneumothrax*
5. Gastrointestinal	Peptic ulcer, haemorrhage Perforation* Pancreatitis Hepatomegaly with fatty infiltration
6. Renal	Nephrocalcinosis* Nephrolithiasis Calciuria* Uricosuria
7. Musculoskeletal	Myopathy and muscle wasting* Osteoporosis and poor bone mineralisation Fracture Avascular bone necrosis
8. Haematological and immunological	Increase total white cell count* Neutrophilia* Monocytopenia Lymphopenia Eosinopenia Erythropoiesis Thrombocytosis Purpura Immunosuppression Infection*
9. Metabolic and endocrine	Somatic growth failure* Hyperglycaemia* Hypokalaemic alkalosis Sodium retention Lipolysis Proteolysis* Increased gluconeogenesis Hypothalamo-pituitary-adrenal axis suppression*
10. Psychological	Psychosis Irritability*

*Side effects of dexamethasone reported in preterm infants.

is a common problem in dexamethasone treated infants and has been reported in the majority of studies.^{16-18 20-22 24 31} As different criteria for the definition of significant hypertension have been used, the exact incidence remains unknown. It is reassuring, however, that in the majority of cases no treatment is required.

A lesser known side effect of corticosteroids on the heart is their potential to cause cardiac muscle hypertrophy.^{35 36} Intraventricular septum and left ventricle free wall thickness were reported to be increased after two weeks' treatment by dexamethasone.³⁵ The hypertrophy of these structures appeared to resolve spontaneously by six weeks when the steroid was stopped.³⁵ No differences were noted in the ejection fraction.³⁵ This phenomenon appears to be completely reversible.

There was also a report suggesting that dexamethasone could induce sinus bradycardia in preterm infants.²⁰ This claim was, however, unsubstantiated by other workers.

(4) RESPIRATORY COMPLICATIONS

It seems almost contradictory to suggest that dexamethasone given to ventilator dependent premature infants for improving their pulmonary function can give rise to pulmonary complications. An increase in the incidence of pulmonary air leaks soon after the start of dexamethasone treatment was probably related to a sudden improvement of pulmonary compliance, leading to overdistension and rupture.¹⁸ This complication is potentially avoidable by vigilant monitoring so that as compliance improves, ventilation pressure can be decreased appropriately.

(5) GASTROINTESTINAL COMPLICATIONS

Gastrointestinal complications that have been associated with corticosteroid treatment include peptic ulcer leading to haemorrhage and perforation, pancreatitis, and fatty infiltration of the liver.

I recently encountered three cases of gastroduodenal perforation in preterm infants treated with dexamethasone.³⁷ The overall incidence is in the region of 2-3%. It was almost always preceded by haematemesis or melaena. In all cases, prompt resuscitation with abdominal paracentesis and early surgical intervention were performed in order to ensure a favourable outcome.

(6) RENAL COMPLICATIONS

Renal complications of corticosteroids are rare and include nephrocalcinosis, nephrolithiasis, uricosuria, and calciuria.

Isolated cases of renal calcification have been identified in premature infants who receive dexamethasone and frusemide treatment³⁸; both are known to be calciuric drugs. As none of the randomised trials looked specifically for its pattern of occurrence or incidence, the true frequency is not known. One can only presume that infants treated

with dexamethasone, especially in conjunction with frusemide, are at an increased risk of developing renal calcification. No data are available on their long term renal function.

(7) MUSCULOSKELETAL COMPLICATIONS

Steroid myopathy, with or without muscle wasting, affects principally the proximal musculature of the limbs. A substantial increase in plasma amino acid concentration³⁹ and a simultaneous increase in urinary excretion of 3-methylhistidine,⁴⁰ soon after dexamethasone was started, was most likely to be due to endogenous myofibrillar protein catabolism. Clinical myopathy in preterm neonates is difficult, if not impossible, to detect and no such case has been reported in the literature so far. Although I have undoubtedly seen poor muscle bulk in babies who have received dexamethasone, I have not encountered any baby who developed frank muscle weakness or paralysis.

Osteopenia and bony fracture are sometimes seen in preterm infants. It is difficult to evaluate the role of steroids in these events as other confounding factors such as immobilisation secondary to the use of muscle relaxants, nutritional rickets, catabolism induced by stress or sepsis, and the use of calciuric drugs may all, in part, be responsible for the poor mineralisation of the bony matrix.

(8) HAEMATOLOGICAL AND IMMUNOLOGICAL COMPLICATIONS

Corticosteroids are capable of substantially increasing the total white cell count by causing marked neutrophilia.⁴¹ Steroid induced neutrophilia is due to a shift of neutrophils from the marginating pool to the circulating pool, an acceleration of the release of mature neutrophils from the bone marrow, and a reduction of the egress of neutrophils from blood to inflammatory sites. Other haematological effects include an enhancement of erythropoiesis, thrombocytosis, monocytopenia, lymphopenia, and eosinopenia.

The anti-inflammatory and immunosuppressive effects of corticosteroids have been extensively investigated. The complexity of the immune system in association with wide variation in response depending on the animal species^{42 43} gives rise to much controversy in assessing the effect of steroids on the human immune function. The current view is that this category of drug has the capability to divert the trafficking, circulation, and availability of inflammatory cell populations to the inflammatory site and possibly in therapeutic dose modify their functions *in vivo*.^{42 43} Interestingly, the anti-inflammatory potency of a particular steroid has little influence on its immunosuppressive effect.⁴⁴ Dexamethasone, which is one of the most potent corticosteroids, has comparatively little immunosuppressive effect.⁴⁴ Although earlier workers reported a high incidence of sepsis in preterm infants treated with dexamethasone,^{15 45} more recent trials suggested that the use of

dexamethasone was not associated with a significant increase in the incidence or change in the pattern of infection.^{18 21 24 31 46}

(9) METABOLIC AND ENDOCRINE COMPLICATIONS

Electrolyte disturbances such as hypokalaemic alkalosis and sodium retention are due to the mineralocorticoid effect of dexamethasone.

Hyperglycaemia is probably among the most commonly reported complications of dexamethasone treatment in preterm babies.^{17 19-21 24 25 31 45} It is easily controllable with insulin or when the steroid dosage and glucose load are reduced. So far, hyperglycaemia has not caused any measurable morbidity.¹⁹

A reduction in insulin activity results in an increase in fatty acid output from adipose tissue and a surge in the total serum triglycerides and cholesterol concentration. Abnormal fat deposition with cushingoid features has undoubtedly been spotted in babies who receive dexamethasone, although it has not been widely reported.

Corticosteroids are known to enhance protein catabolism. Babies treated with dexamethasone showed a generalised and substantial increase in amino acid concentration,³⁹ with a coincidental increase in urinary excretion of 3-methylhistidine, which in the absence of meat protein in the diet suggested endogenous myofibrillar protein catabolism.^{39 40} This phenomenon appears to be dose related. Tyrosine and phenylalanine, however, behaved differently and did not demonstrate an increase in plasma concentration during steroid treatment. The risk of hyperphenylalaninaemia toxicity is therefore minimal.

Growth impairment has been reported in preterm infants during dexamethasone treatment for BPD.^{18 19 23 25} Interruption of growth in this early period is potentially critical for it may have a permanent influence on the 'programming' of somatic growth in later life. Recent data suggest that the effect of growth retardation is likely to be transient and normal growth pattern resumes after dexamethasone is stopped.¹⁹ So far, there has not been any long term follow up assessment to monitor somatic growth in these babies into their early childhood.

Perhaps the most feared side effect of corticosteroid treatment is hypothalamo-pituitary-adrenal axis suppression. The adrenal glands are undoubtedly suppressed during the treatment period but this effect appears to be transient. Within a month after steroid treatment is discontinued, most babies appear to have regained their adrenal responsiveness.⁴⁷ None of the babies show any signs of clinical or biochemical adrenal insufficiency.⁴⁷

(10) PSYCHOLOGICAL DISTURBANCES

'Irritable' behaviour was observed in a small proportion of infants with BPD within the first few days of dexamethasone treatment. This pattern of behaviour promptly reverted to normal after a reduction in dosage.³¹ Although conceivably steroid related mood changes and psychosis could have occurred in preterm infants as in adults, interpretation of such subjective signs must be viewed with caution as other confounding factors such as respiratory discomfort, pain, and gastritis might have contributed to their occurrence.

Balancing benefits and risks

As with any new treatment, the decision whether to start an infant on dexamethasone rests entirely on the perception of the benefits and risks of the treatment (table 3). A clinician may put more emphasis on one factor as opposed to the others and finalise his decision one way, while another clinician may take an opposite view. So far, there are no absolute guidelines on which babies to treat or when to treat them. Furthermore, the optimum dosage of dexamethasone, the most desirable schedule, and duration of treatment have not been fully verified. Hence, the above recommendations are, to a certain degree, dependant upon subjective impression and personal experience of the drug.

In my opinion, dexamethasone has a definite role in the management of BPD by shortening the duration of mechanical ventilation. The very limited number of intensive care cots can, therefore, be used to care for more sick babies. This translates into a substantial financial saving for the health service per baby treated. The elimination of the ventilator also means greater freedom for parents to handle their baby, thus promoting close parent-child bonding. Furthermore, by making significant therapeutic progress, the morale of the caregivers working under the stressful conditions of the neonatal unit is boosted. Above all, the discontinuation of positive pressure ventilation removes the risk of ventilation related complications such as pulmonary air leaks, pneumonia, and further barotrauma, which acts as a continuing stimulus for the inflammatory cascade.

With regard to the negative side of steroid treatment, none of the randomised trials performed to date has managed to show an improvement in the mortality rate of steroid treated infants compared with controls. Some of the side effects that have been reported in preterm infants are undoubtedly over exaggerated. In particular, the early reports on the incidence of severe infections^{15 45} have now been challenged by later trials that report no appreciable increase in frequency nor any change in the pattern of occurrence.^{18 21 24 31 46} The total white cell and neutrophil count are

Table 3 The benefits and risks of dexamethasone treatment

Benefits	Risks
1 Shortening the duration of assisted ventilation	1 Hypothalamo-pituitary-adrenal axis suppression
2 ?Shortening the duration of supplemental oxygen treatment	2 Enhanced catabolism, hyperaminoacidaemia, and somatic growth failure
3 ? Shortening the duration of hospitalisation	3 Gastroduodenal perforation
4 ? Favourable neurodevelopmental outcome	4 Hypertension
	5 Hyperglycaemia

affected by dexamethasone and are not reliable predictors of infection but plasma C reactive protein concentration is unaffected and remains a good indicator for monitoring neonatal sepsis.

In the past few years, even the less common and infrequent side effects of steroids such as gastrointestinal perforation are increasingly being recognised.³⁷ Therefore, neonatal clinicians must be equipped with the knowledge and must be prepared to encounter even the lesser known and rare complications of dexamethasone treatment.

Perhaps, in future, the use of more specific treatments such as monoclonal antibody to TNF- α and inhaled corticosteroids will emerge to be better treatment for BPD, with fewer side effects. Until more is known about the safety and beneficial effects of systemic steroids in this group of patients, in particular their influence on long term neurodevelopmental and pulmonary outcome, indiscriminate use should be prohibited. I believe the prudent course is to restrict their use to ventilator dependent infants with moderate to severe BPD.

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