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Chronic lung disease of prematurity: are we too cautious with steroids?

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Abstract Encompassed by the term chronic lung disease (CLD) of prematurity is a sequence of pathophysiological processes ranging from acute inflammation and its resolution to remodelling and growth. There is good evidence for clinical and biological effects of parenteral corticosteroid therapy at each stage in the disease process. A number of questions remain to be resolved: can risk prediction be refined to permit trials of prevention; what is the minimum effective dosage regime; are topical corticosteroids effective; what are the long-term effects on lung growth and development and indeed, is the long-term prognosis of CLD affected by corticosteroid therapy? It is prudent to be cautious with steroids until these questions are answered.

Key words Infant pulmonary function · Bronchoalveolar lavage Cytokine · Clinical trials

Abbreviations *BAL* bronchoalveolar lavage · *BPD* bronchopulmonary dysplasia · *CLD* chronic lung disease IL-6 interleukin-6 · *MDI* metered dose inhaler · *RDS* respiratory distress syndrome

Introduction

The use of corticosteroids in the management of chronic lung disease (CLD) of prematurity is a relatively recent innovation [38]. Before that, maternal corticosteroid therapy had become widely accepted for the prevention of respiratory distress syndrome (RDS) in very low birthweight babies [17], although there is in fact no convincing evidence that the prevalence of CLD has been significantly reduced by antenatal corticosteroids [17]. Nevertheless, the apparently benign nature of this treatment for the fetus and newborn infant may have provided encouragement to those who recognised that in CLD, the sequence of acute inflammation and fibrotic healing might be a suitable situation for trials of steroid therapy.

Chronic lung disease of prematurity

Although studied in great detail in animal models [19], an understanding of the histopathology and cell biology of CLD in human infants is clearly hampered by the fact that tissue is only available at necropsy from the very sickest infants. It is important however to try to define the disorder and to identify the various clinico-pathological phases through which infants pass, in order to be able to make sense of epidemiological and therapeutic studies [54].

The narrow definition of bronchopulmonary dysplasia (BPD) [46] suggests an all-or-none situation. In fact, CLD represents a continuum of severity from severe respiratory failure with typical radiological features at one extreme, to the mildest symptoms (or even asymptomatic minor physiological disability) at the other. There is also a temporal dimension to the evolution of disease. From a practical standpoint, CLD might be defined by the many features which suggest delayed resolution of acute respiratory disease, for instance failure to extubate a baby with severe RDS by 1 week of postnatal age, classical BPD at 28 days of age or continued respiratory problems after discharge from the neonatal unit. The latter can be predicted with some confidence at around 36 weeks gestational age [53]. Whatever definitions are applied, they

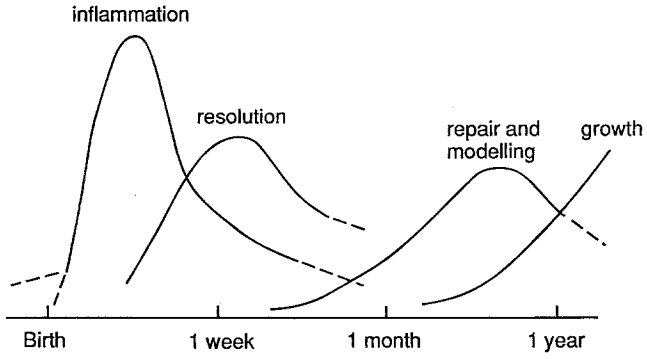

Fig. 1 Clinicopathological phases in the evolution of neonatal lung disease and its resolution. Disturbance of these phases, either by their persistence or by incomplete resolution, constitutes CLD

must be clearly described in clinical trials of corticosteroid therapy.

There are several overlapping phases in the resolution of neonatal lung disease, each with characteristic pathological features (Fig. 1). The neat progress from each to its successor may be disturbed by intercurrent infection, gastro-oesophageal reflux, localised complications such as pulmonary interstitial emphysema or by underlying congenital abnormalities. Failure of complete resolution of each phase with incomplete restitution of normal lung structure and function, constitutes CLD. The four phases will be briefly described:

1. *Inflammation* is a feature of acute RDS, even in the absence of premature rupture of the membranes [4, 47]. Widespread epithelial necrosis and type II alveolar cell hyperplasia are found. A wide variety of cytokines and other biologically active agents are detectable in bronchoalveolar lavage (BAL) fluid, possible agents in the subsequent development of BPD [13, 28, 59, 62].

2. The *resolution* of inflammation is a crucial but little studied process [29]. Persistence of neutrophilia is associated with CLD [4, 47] and at this stage BAL reveals a host of cytokines and inflammatory mediators including platelet derived growth factor, tumour necrosis factor α, leukotrienes, elastases, fibronectin and histamine [9, 25, 41, 43, 47, 58, 60, 61, 63, 68]. There is persistently increased epithelial permeability [33]. This period of activity may be crucial in the development of CLD. It corresponds to the time, at about 1–4 weeks of age, when classical BPD becomes apparent. The correlation between BAL and lung histology has not been adequately explored.

3. *Repair and remodelling* can only be studied in postmortem material. With the resolution of inflammation, healing leads to alterations in the morphology of many lung structures, including: airway epithelial metaplasia; sub-mucosal glandular hypertrophy; airway smooth muscle hypertrophy; alveolar loss; interstitial fibrosis and excess elastin formation; altered pulmonary arteriolar structure [24, 31, 32]. Alveolisation is clearly disrupted, so that fewer, larger alveoli are found at postmortem in fatal cases of CLD in infancy [32]. One can only speculate that less extensive abnormalities occur in milder cases. This stage of CLD corresponds roughly to infancy, when symptoms may vary from severe, oxygen dependent respiratory failure and pulmonary hypertension to chronic or episodic cough and wheeze.

4. The final phase of lung *growth* has not been properly addressed in human infants, but hase potentially life-long consequences [7]. Thus prevention or early management of CLD may be critical.

Corticosteroids in neonatal chronic lung disease

Pharmacology

The effects of corticosteroids on the lungs can be considered at the molecular or cellular level [56], at the functional or physiological level and at the level of clinical disease. There are data on all these outcome measures of corticosteroid therapy in preterm infants. The common theme of most studies is the anti-inflammatory action of corticosteroids [56]. There are however several other potentially relevant actions, some studied only in animal models, including enhancement of β_2-receptor density, increased transduction of the genes for several antioxidant enzymes, enhanced surfactant production and suppression of inducible nitric oxide synthase [5, 8, 39, 64].

Administration and dosage regimes

Dexamethasone is the most popular corticosteroid in neonatal practice and parenteral (usually intravenous) administration is the usual route. There has been no attempt to carry out dose-ranging studies and although the variation in starting dose between studies is small, 0.5–1 mg/kg body weight per day in divided doses, the duration of therapy varies widely from 3–42 days. A comparison of different regimes was carried out in only one study [18]. Despite known differences between corticosteroids in the degree of penetration into the lungs after parenteral administration [11], no study of this important aspect of therapy has been reported in young infants.

There is no a priori reason to suppose that, topical steroid therapy by aerosol is likely to be effective in CLD, but the potential advantage of this route of administration is a greater ratio of pulmonary:systemic effect. One hurdle to be overcome is the method of administration. The delivery of drugs by metered dose inhaler (MDI) into a small volume spacer device attached to the endotracheal tube is far more efficient than jet nebulisation [3, 27, 52]. Three preliminary but encouraging reports of aerosol steroid therapy for CLD have been published [21, 37, 50].

There is a 40-fold difference in dose between two of the studies! Paradoxically, it may be possible to administer size-related lung doses to neonates far in excess of those normally used for older asthmatic subjects, with potentially greater local toxicity. Again, dose regimes and the pulmonary distribution of aerosols have not been adequately studied in neonates.

Clinical trials and observations

Preventive use of corticosteroids

Apart from antenatal use which, although reducing the incidence of RDS does not affect the overall incidence of CLD [17], only one study has investigated the possibility that early neonatal dexamethasone therapy (within 12 h of birth) given to intubated infants with RDS might prevent CLD [67]. This study raises an interesting problem. Although the incidence of CLD in survivors (defined as classical BPD) was no different in this well-conducted double blind trial between treated (8/25) and control (12/21) infants, when early deaths were taken into account healthy survival at 28 days was significantly greater in treated (17/28) than in control (9/29) infants ($P < 0.05$). By enhancing survival, thereby creating a greater opportunity for the development of CLD, a narrow interpretation of preventive studies may underestimate their potential benefit.

There was no attempt to select infants at risk in this study. Refinement of early postnatal risk prediction would clearly help [53, 55, 57], by minimising the number of infants exposed to potentially toxic therapy.

Table 1 Effects of dexamethasone on lung mechanics in intubated infants with CLD

Reference number	*n*	Controlled (C) or sequential (S) observations	Respiratory resistance	Respiratory compliance
68	7 + 7	C	[a]	↑
26	7	S	↓	↑
50	5	S	↓	↑
6	7	S	–	↑
12	7	S	↓	↑
Typical changes in 24–72 h:			30%	60%–70%

[a] Significantly increased expiratory flow by the forced deflation technique

Systemic corticosteroids in established CLD (BPD)

Ehrenkranz and Mercurio [22] have thoroughly reviewed the management of BPD in general and the use of corticosteroids in particular. Nine randomised controlled trials of parenteral or oral dexamethasone have been reported for infants aged 2–6 weeks postnatal age [6, 15, 18, 30, 35, 38, 45, 48, 68]. All except two [15, 45] were devoted exclusively to intubated babies. The UK collaborative trial, by far the largest, with 285 babies, covered a wide clinical spectrum of disease. The main outcome measures in most trials were: speed of extubation and duration of oxygen therapy. Extubation was clearly facilitated in all but one study [35], but the overall duration of oxygen therapy and of hospitalisation was in general unaffected.

Pulmonary mechanics have been reported in a number of small, mainly sequential observations (Table 1) [6, 12, 26, 50, 68]. Individually, these studies have major flaws, but their consistency is remarkable. Within 12–72 h, falls in respiratory resistance of about 30% and increases in compliance of 60%–70% are typically seen.

Attempts to understand the mechanism of corticosteroid action in CLD have lead to a bewildering number of measurements of cytokines and other cell products in BAL fluid or tracheal aspirate (Table 2). This is definitely a growth area. Sadly, the majority of observations were not designed to answer any useful hypotheses and the stage seems to be set to repeat all the mistakes of the mediator-era of asthma research! Again there are method-

Table 2 Some reported effects of dexamethasone on cytokines and other local products in tracheal aspirate or BAL fluid in CLD

Cell product	Reference number	Controlled or sequential observations	*n*	Effect of dexamethasone
Interleukin-6	61	S	41	↑
Tumour necrosis factor α	43	S	28	±
Platelet derived growth factor (B)	63	S	41	↓
Fibronectin	60	S	45	↓
	25	S	9	↓
	68	C	9 + 8	↓
Elastase/antiprotease	25	S	9	↓
	68	C	9 + 8	↓
Histamine	9	C	16 + 16	↓

ological defects in many studies: inadequate control data, sequential observations, lack of attention to the expression of BAL fluid mediator concentrations (by reference to a reliable denominator) and very variable and small patient groups. The most comprehensive and carefully conducted study showed parallel changes in BAL neutrophil cell counts, cell products, lung mechanics and clinical status within 3 days of starting dexamethasone therapy in a randomised, controlled trial [68].

Topical corticosteroids in established CLD (BPD)

The three observational studies of topical corticosteroid therapy for intubated, mechanically ventilated infants with CLD [21, 37, 50] cannot do more than encourage those who wish to establish properly designed clinical trials. The potential range of devices, drugs and doses is huge, although we now have sufficient data for human and model lung experiments to devise regimes for clinical trial purposes [3, 27, 52].

Corticosteroids for older infants and children

Very little data are available to support personal clinical observations that symptomatic infants with oxygen-dependent CLD benefit from topical corticosteroid therapy. In our own practice 19 out of 58 babies discharged home on oxygen therapy have been apparently successfully treated with topical budesonide or beclomethasone administered by MDI, Aerochamber and facemask. In a formal clinical trial, symptomatic infants who were born prematurely, benefited by a reduction in wheeze and cough during topical corticosteroid therapy (beclomethasone 100 μg twice daily for 6 weeks by MDI, spacer and facemask) [69]. However, symptomatic 7-year-old schoolchildren of low birth weight with increased bronchial responsiveness did not benefit from a similar regime, suggesting that at that age, airway inflammation did not contribute to their disease [14].

Other uses of corticosteroids for neonatal lung disease

Two randomised trials have investigated the efficacy of very short courses of dexamethasone in weaning from mechanical ventilation. A single dose 30 min before extubation had no benefit [23] whereas three doses of 0.25 mg/kg per 8 h, commenced 4 h before extubation, was beneficial by three criteria: successful extubation improved lung mechanics and reduction in subsequent stridor [16].

Adverse effects of corticosteroids

Brief and probably insignificant systolic hypertension, hyperglycaemia and neutrophilia are reported in many of the dexamethasone trials. Of more concern is the evidence of adrenal suppression of up to 1 month's duration even after 1 week of therapy [2, 34].

Gastro-intestinal perforation has been reported [44, 49]. Whether this rare complication can be safely prevented by the routine use of H_2 blocking agents during dexamethasone therapy [36] remains to be investigated.

One of the most worrying potential effects of corticosteroids on the growing lung is suppression of alveolar development. Research into the effects of fetal corticosteroids on subsequent lung growth in animal models is inconclusive, with studies showing persistent [10], transient [42] or no effect [1] on lung growth. There are certainly effects on somatic growth and lung morphology from brief exposures of neonatal rats to modest doses of dexamethasone [20, 40]. Measurements of lung function in infants and children exposed to antenatal dexamethasone do not suggest any persistent adverse effects [65, 66]. However, the studies are small, open to bias and depend on an assumption that lung "function" is equivalent to lung "growth".

Unresolved problems

Clinical trials

The data available suggest that corticosteroids are effective. Information is needed on the risk/benefit ratio of preventive therapy and on minimum dose regimes. Better characterisation of patients and some attempt at risk prediction to allow more selectivity would be advantageous.

The efficacy of topical steroids for early disease is certainly not yet established. Any trials must address the problems of administration and pulmonary dose and distribution. More research is needed in this area in order to avoid costly clinical trials of "placebo" therapy.

Simple short-term measures of efficacy which are available to all neonatologists, such as ventilatory efficiency index, may allow ineffective therapy to be withdrawn early, avoiding unnecessary adverse effects. There are at present no such predictors.

Adverse effects

There are real concerns about the effects of corticosteroids on lung growth. Local concentrations of topical corticosteroids given by MDI and spacer to intubated babies may be very high and need to be measured. Such local peaks might have adverse effects on lung development

at a critical period of alveolisation. Similarly, later therapy for symptomatic, chesty infants could affect lung growth with life-long adverse consequences. It would be rash to try to predict, on the basis of present knowledge.

Novel corticosteroid derivatives promise anti-inflammatory effects without adrenal suppression [51].

Basic mechanisms

We need to explore the cellular basis of CLD in more detail. Corticosteroids are blunt tools which continue to serve us well in default of more specific agents and more precise targets.

Conclusion

In answer to the question posed by the title of this article: NO we are not too cautious with corticosteroids, given our present knowledge. It is too early to write comprehensive clinical protocols for corticosteroid therapy either for the prevention or treatment of neonatal CLD. Within limits however these drugs play an important part in the management of ventilator dependent preterm babies with the earliest stages of chronic lung disease. More randomised controlled trials are needed, with the power to answer specific questions about short-term and long-term risks and benefits.

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