CURRENT TOPICS

Effects of antenatal and postnatal corticosteroids on the preterm lung

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It is nearly 25 years since Liggins and Howie first reported the maturational benefits of antenatal corticosteroids given to mothers of preterm infants.[1] They reported reduced incidence of respiratory distress syndrome (RDS) in preterm infants delivered to mothers treated with antenatal steroids. Since then, several other studies have reported similar benefits for antenatal corticosteroids. Indeed, Crowley[2] has reported a meta-analysis of 15 randomised trials, conducted between 1972 and 1994, which studied the use of antenatal corticosteroids in preterm labour. Overall, the incidence of RDS was halved in infants delivered to mothers who had received antenatal corticosteroids compared with those born to mothers treated with placebo. Secondary analysis clearly showed that when antenatal corticosteroids are given between 24 hours and 7 days before delivery, the odds ratio is 0.35 (95% CI 0.26–0.46). This is reduced to 0.8 (95% CI 0.56–1.15) if antenatal corticosteroids are given at less than 24 hours before delivery, and to 0.63 (95% CI 0.38–1.07) if given more than seven days before delivery. Clearly, antenatal corticosteroids require at least 24 hours to exert their effects.

Clinical trials of postnatal systemic corticosteroids in established chronic lung disease of prematurity (CLD) have been thoroughly reviewed by Ehrenkranz and Mercurio.[3] At least nine randomised controlled trials of parenteral or oral dexamethasone have been reported for infants aged 2–6 weeks of postnatal age.[4–12] All except two[5 10] were devoted exclusively to intubated babies. The UK collaborative trial, one of the largest with 285 babies, covered a wide clinical spectrum of disease.[5] The main outcome measures in most trials were speed of extubation and duration of oxygen treatment. Extubation was clearly facilitated in all but one study,[8] but the overall duration of oxygen treatment and of inpatient stay were generally unaffected. Although postnatal corticosteroids may facilitate weaning from mechanical ventilation, the optimal timing of treatment is uncertain. Some evidence points to improved benefits if given early.[13 14] As with antenatal corticosteroids, the mechanisms involved in the improvement in pulmonary function in CLD are currently poorly understood.

Effects of corticosteroids on lung growth
Studying the specific effects of corticosteroids on human infants is difficult because diseases such as CLD may themselves affect lung growth.[15 16] Most studies have therefore concentrated on animal models to determine both beneficial and adverse effects of these drugs on lung growth. When given antenatally, corticosteroids accelerate lung maturation.[17] The normal thinning of the double capillary loops, to form the thin gas exchanging walls of alveoli, is accelerated, resulting in rapid alveolisation.[18] The maturation of surfactant producing type II pneumocytes is also speeded up.[19] Although the alveolisation occurs rapidly as a result of the corticosteroids, the total number of alveoli is decreased. This was reported by Beck *et al*, who treated preterm Rhesus monkeys (between 66% and 85% of term) with antenatal corticosteroids.[20] This decrease in eventual numbers of alveoli is partly due to suppression of the formation of secondary septa, a necessary step in the division of alveoli. These observations of accelerated alveolisation with ultimate reduction in total number of alveoli has also been reported by Plopper's group.[18] They also showed decreased body weight in Rhesus monkeys treated with antenatal steroids. This reduction in body weight was most obvious when the drugs were used early in gestation than when given later, and when higher doses of corticosteroids were used. Thus antenatal corticosteroids improve alveolisation in preterm animals at a critical time when delivery may result in severe acute respiratory failure. However, lung growth and body weight may be affected in the long term by such treatment.

The effects of postnatal steroids are similar and have been proved in some elegant studies by Burri's group.[21] When dexamethasone was given postnatally to newborn term rats for the first two weeks of life, acceleration of the alveolar wall thinning and microvascular maturation were seen, together with partial suppression of formation of secondary septa. A week after treatment had stopped, the accelerated lung maturation was partially reversed with the inter-airspace septa regressing towards a more immature thickened state. A secondary burst of alveolisation followed, but the eventual result of postnatal corticosteroid treatment was an

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"emphysematous" lung with larger and fewer airspaces.

Although animal models suggest that alveolisation may be affected both in prenatal and postnatal corticosteroid treatment, adverse effects in humans have not been reported. Morphometric study of the lungs of living humans is not feasible, but small observational physiological studies of children at a mean (SEM) age of 7.5 (0.3) years born to mothers who had received antenatal steroids suggests that such treatment does not adversely affect pulmonary function which is an insensitive indicator of lung growth.[22] Similarly, antenatal corticosteroids do not seem to have a clinical effect on somatic growth[23] or neuro-development.[24]

Effect of antenatal and postnatal steroids on surfactant

An obvious target for the improved respiratory outcome in preterm infants after antenatal corticosteroid treatment is the surfactant system. Pulmonary surfactant, which is produced by type II pneumocytes, is composed of about 90% lipids—mainly phospholipids—and 5–10% surfactant proteins.[25] The phospholipids have surface tension reducing properties, while the surfactant proteins are important in regulating surfactant function and metabolism, and may also have an immunomodulatory role.

As antenatal corticosteroids accelerate maturation of type II pneumocytes, enhancement of the pulmonary surfactant system is expected. Glucocorticoids increase mRNA of surfactant proteins B and C in rats[26] and human fetal lung explants[27] in a dose dependent manner. However, data for surfactant protein A (SP-A) from animal models are at best confusing and at worst conflicting. SP-A has a major role in the organisation of phospholipids in tubular myelin and in the regulation of phospholipid secretion and reuptake.[25] In human fetal lung explants glucocorticoids have both inhibitory and stimulatory effects on the concentration of SP-A and its mRNA, which are dose dependent.[28] Dexamethasone stimulates SP-A transcription but the same concentrations decrease total SP-A mRNA because of the shortened half life of the mRNA.[28] To add to the complexity, the effects of corticosteroids differ according to the stage of fetal lung development.

Such observations are difficult to apply to the clinical situation. The most convincing data to date for the role of dexamethasone in improving SP-A concentrations in tracheal fluid from ventilated infants were recently published by Wang *et al*.[29] Infants receiving early dexamethasone had increased SP-A and SP-D in tracheal fluid which was parallelled by an improvement in respiratory status and a decrease in albumin in tracheal fluid compared with infants who received placebo. By contrast, a clinical study by Ashton *et al* did not observe an improvement in the hydrophobic components of surfactant, assessed by fractions of dipalmitoylphosphatidylcholine (DPPC) in bronchoalveolar lavage fluid, when infants at high risk of developing CLD were treated with

corticosteroids at 14 days of age.[30] This lack of improvement is very likely to be due to the late treatment with corticosteroids. There are no similar data for infants treated early with corticosteroids. In vitro studies, using human fetal lung explants, suggest that treatment with glucocorticoids accelerates the rate of incorporation of choline into DPPC and increases both the concentration and saturation of phosphatidyl choline (PC).[31] These changes were accompanied in part by the accelerated appearance of lamellar bodies in type II pneumocytes.

Thus the effects of corticosteroids on the fetal and newborn lung suggest that components of the surfactant system are generally enhanced, but the drugs have differential effects depending on the dose and stage of lung development. Additional work, particularly on human infants, such as the study conducted by Wang *et al*, is essential to determine the clinical importance of in vitro studies on the human preterm lung.

Effects of corticosteroids on the antioxidant system

Antioxidants in neonatal lung disease have recently been reviewed.[32] Hyperoxic acute pulmonary injury is promoted by the formation of oxygen free radicals. These include hydroxyl groups, hydrogen peroxides, and superoxides. Such oxidative damage is prevented by antioxidant enzymes which include superoxide dismutase, catalase, and enzymes of the glutathione redox cycle (glutathione peroxidase, glutathione reductase, and glucose-6-phosphate dehydrogenase), and by non-enzymatic antioxidants, including glutathione, vitamins A and E, transferrin, uric acid and caeruloplasmin. The expression of the antioxidant enzymes is low in preterm rats, rabbits, hamsters and guinea pigs compared with term animals.[33–35]

Prenatal treatment of pregnant rats with dexamethasone enhances fetal lung antioxidant enzymes together with a parallel acceleration in fetal surfactant production.[36] Improved survival to hyperoxic exposure may provide a more convincing argument for a role for antioxidant enzymes in improving respiratory outcome in neonates whose mothers had been treated with corticosteroids. This question was addressed by Frank's group[37] who showed improved survival of full term newborn rat pups exposed to hyperoxia from birth, having been delivered to mothers treated with antenatal corticosteroids. At 7 days, 97% of the antenatal dexamethasone group had survived compared with only 71% in the placebo group. Survival at 14 days was 55% and 31% in the treated and untreated groups, respectively. However, antioxidant enzymes were increased at 24 hours in the group treated with corticosteroids but were similar to those of the untreated group after 24 hours of age. As survival remained better in the group treated antenatally, it may be that it is the rate of increase in antioxidant enzymes rather than simple increases in these enzymes which is more important. Prematurely delivered rat pups were studied by Keeny *et al*,[33] who showed

that the survival of the preterm pups in the group treated antenatally was significantly better than in the untreated group at 24 hours of age (91% *vs* 57%). Increases were seen at 24 hours of age in antioxidant enzymes in the treated group, as in Frank's study, with no significant differences being seen after this age in both the treated and untreated groups. However, Keeny and colleagues were unable to demonstrate improved survival in term newborn pups exposed to hyperoxia in either treated or untreated groups.

There are no equivalent data for the role of antenatal corticosteroid treatment in humans, except for exposure of human fetal lung explants which seem to suggest that corticosteroids may enhance the expression of antioxidant enzymes. Antenatal treatment with corticosteroids in women probably improves the concentrations of antioxidant enzymes in the fetus with consequent improved tolerance to postnatal hyperoxic exposure.

Effects of corticosteroids on mediators of inflammation

Corticosteroids have many different actions, including effects on the surfactant system, antioxidant enzymes, and on both somatic and lung growth of the fetus and newborn infant. In addition, corticosteroids are among the most potent anti-inflammatory agents known. Our understanding of the mechanisms which may be important in the pathogenesis of chronic lung disease of prematurity is slowly improving.[38–40] Pulmonary inflammation is maximal at 7–10 days of age in infants who develop CLD, evidenced by an increase in neutrophils,[41–43] neutrophil elastase,[43 44] the pro-inflammatory cytokines TNF α, interleukins 1 and 6,[45–47] and in products which reflect neutrophil recruitment to the lung—namely, soluble adhesion molecule ICAM-1[43–48] and the potent neutrophil chemotactic factor IL-8[43 49] in bronchoalveolar lavage fluid obtained from infants who develop CLD. Only a few studies with small numbers have examined the effect of corticosteroids on mediators of inflammation. Gerdes *et al* have shown a decrease in elastase activity in tracheal fluid obtained from venti-

Key messages

Ante- and postnatal corticosteroids:
- improve respiratory outcome in preterm infants
- accelerate lung maturation
- increase surfactant protein and phospholipid production
- improve antioxidant status and activity
- decrease pro-inflammatory cytokines
- adversely affect long term lung growth in some animal studies.

lated infants receiving dexamethasone compared with controls treated with saline.[44] Yoder and colleagues reported an improvement in neutrophils in tracheal fluid obtained from ventilated infants treated with corticosteroids which was matched by an improvement in pulmonary function.[50] Further small descriptive studies have shown that mediators of inflammation may be decreased by the use of corticosteroids.[51 52] Interestingly, most units treat oxygen dependent, mechanically ventilated infants with corticosteroids at 2–3 weeks of age. However, if corticosteroids are to exert maximal anti-inflammatory effects it may be necessary to treat those babies at risk of developing CLD earlier than the pulmonary inflammation which peaks at 7–10 days of age.[38] There is some clinical evidence to support this hypothesis[13 53] but this was not supported by a recent study from Israel.[54]

There are currently no data on the effects of antenatal steroids on mediators of inflammation or fibrosis in the human newborn lung. Our previous study examining the concentration of the potent pro-fibrotic growth factor transforming growth factor β 1 (TGF-β$_1$) in bronchoalveolar lavage fluid did not shown any influence of antenatal treatment with corticosteroids.[54]

Conclusions

There are convincing data to support the use of antenatal corticosteroids in improving the respiratory outcome of newborn infants, especially those at greatest risk of developing respiratory failure. The current data suggest that this improvement may be due to enhanced expression of proteins and phospholipids of the surfactant system and enzymes of the antioxidant systems (table 1). Nevertheless, caution is needed, as the scanty data that are available in animal models suggest that lung growth as well as somatic growth *may* be adversely affected. This may be of particular importance in those women who receive repeated doses of dexamethasone when preterm labour is repeatedly threatened.

Some recent data by Wang *et al* suggest that postnatal corticosteroids may increase some of the proteins in the surfactant system but additional similar studies are required to identify the exact mechanisms of corticosteroid action. Studies on the mediators of inflammation suggest that corticosteroids may dampen the pulmonary inflammation that is seen in infants who develop CLD. Only by further elucidating

Table 1 Possible mechanisms for effects of ante- and postnatal corticosteroids on fetal and newborn lung

	Antenatal corticosteroids	Postnatal corticosteroids
Lung growth	Accelerated lung maturation	Accelerated lung maturation
	Accelerated thinning of double capillary loops	Accelerated thinning of double capillary loops
	↓ Secondary septal formation	↓ Secondary septal formation
	? Decreased final alveoli number	? Decreased final alveoli number
	↓ Body weight	
Surfactant	↑ Lamellar bodies in type II pneumocytes	↑ SP-A, SP-D
	↑ SP-B, SP-C, SP-D	?↑↓ SP-B, SP-C
	↑↓ SP-A depending on gestation	?↑ Choline incorporation into DPPC
	↑ Choline incorporation into DPPC	?↑ Concentration of PC
Antioxidant enzymes	Improved survival in rat pups	? ↑ Antioxidant enzyme activity
	↑ Antioxidant enzyme activity	
	↑ Antioxidant activity	
Inflammation	Unknown	↓ Neutrophils
		↓ Tracheal fluid elastase
		↓ Proinflammatory cytokines
		? Effect on growth factors

the specific actions of both ante- and postnatal corticosteroids can more precise treatments for neonatal respiratory failure be developed.

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