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Surfactant replacement therapy for non-respiratory distress syndrome neonatal respiratory disease – research or clinical application?

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Abstract Research studies have highlighted both physiological and pathological evidence to incriminate surfactant abnormality and/or deficiency in many neonatal respiratory diseases. Data from animal models and clinical studies support the concept that surfactant replacement therapy (SRT) may have a role to play in such problems. There is now, therefore, a need to perform further randomized controlled trials to assess the appropriate clinical application of SRT in non-respiratory distress syndrome neonatal respiratory disease.

Key words Surfactant replacement therapy · Neonatal respiratory disease

Abbreviations *a/A* alveolar/arterial · *ARDS* adult respiratory distress syndrome · *CDH* congenital diaphragmatic hernia · *ECMO* extracorporeal membrane oxygenation · *MAS* meconium aspiration syndrome · *RDS* respiratory distress syndrome · *SP-A* surfactant protein A · *SRT* surfactant replacement therapy

Introduction

Surfactant replacement therapy (SRT) now has a well recognized role in the therapy of respiratory distress syndrome (RDS). Despite widespread use of SRT in patients with RDS, there are no multicentre randomized trials investigating its efficacy in "non-RDS" neonatal respiratory disease. The purpose of this review is, therefore, to explore the rationale for the use of SRT in certain "other" neonatal respiratory problems and assess data which are available from animal and clinical studies. The aim being to assess if sufficient information is already available to determine whether, in non-RDS neonatal respiratory disease, SRT remains a research tool or has a clinical application.

Properties of surfactant

In RDS, the ability of surfactant to improve alveolar stabilization, in part due to reduction in surface tension, is particularly important. Surfactant, however, has numerous other functions [3] thus its use should be considered for non-RDS neonatal respiratory diseases. Surfactant stabilizes small airways, as well as alveoli, preventing their collapse and consequent air trapping. It also inhibits pulmonary oedema formation and improves fluid dispersal in small airways [11]. These latter functions are likely to be of importance in the treatment of adult respiratory distress syndrome (ARDS) and severe respiratory failure of other causes. Surfactant can increase the transportability of mucus, reducing its rigidity probably by decreasing the viscosity and elasticity; it also increases mucus hydration and has an anti-glueing effect [17]. In a dose dependent fashion, surfactant increases ciliary beat frequency by approximately 10% [8]. Anti-bacterial activity has also been demonstrated; improved *Staphylococcus aureus* killing in the rat [10] and increased phagocytosis in both the human and rat [14]. The surfactant protein A (SP-A) is an opsonin for phagocytosis of the herpes virus. These functions suggest SRT might have a role in therapy for pneumonia and meconium aspiration syndrome (MAS). Surfactant has some anti-inflammatory effects including re-

ducing secretion of interleukin-1, interleukin-6 and tumour necrosis factor by monocytes [18] and macrophages and decreasing lymphocyte proliferation, but in contrast it increases macrophage migration. Surfactant can cause smooth muscle relaxation, reducing ileal contraction due to angiotensin II, there are, however, no data regarding its effect on bronchial smooth muscle. These latter properties suggest SRT might be useful in the treatment of asthma or chronic bronchitis. Neonatal chronic lung disease mimicks some aspects of those diseases cited above, that is airways obstruction, bronchial alveolar collapse, and mucus and surfactant abnormalities; thus SRT might be considered for affected patients.

Pneumonia

Bacterial, viral and aspiration pneumonias all have features of surfactant deficiency or abnormality which are improved in animal models by SRT. Broncho-alveolar lavage studies have demonstrated that bacterial pneumonia is associated with both a reduction in surface tension, SP-A and lung lavage phospholipids and surfactant dysfunction. SRT in an animal model was able to improve lung compliance to normal levels. Mycoplasma pneumonia also has features resembling surfactant deficient RDS; reduced lung compliance, abnormal pressure-volume curves, and an increase in palmitic acid. Influenza virus reduces the phospholipid content of type II pneumocytes in a mouse model, in which SRT improved survival from 0% to 75%. In an animal model, acid aspiration resulted in pulmonary oedema, reduction in surfactant function and hyaline membrane formation; in that model SRT improved lung recoil. The clinical data available on SRT in pneumonia, however, are not particularly encouraging. In low birth weight infants, although treatment with Alveofact resulted in an initial improvement in oxygenation, the inspired oxygen concentration was back to the baseline level within 12 h. Of the 15 infants so treated, 10 died, 4 of respiratory failure [6].

Meconium aspiration syndrome

Meconium displaces surfactant from the alveolar surface and inhibits surfactant's surface tension lowering function. That latter inhibitory action can be overcome if a sufficiently high dose of SRT is used [19]. Piglet and lamb models of MAS have been created by instilling human meconium slurry into the lungs. In such models, the success of SRT has been mixed. Although differences in oxygenation were experienced between groups treated with natural surfactant compared to saline lavage or suction alone, no significant radiological or pathological differences were noted [15]. In a lamb model, the improvements in oxygenation seen in the 1st h after treatment were not associated with improvements in compliance, but a deterioration in resistance [2]. Clinical experience to date suggests only a proportion of infants with MAS will respond to SRT. Of 20 infants with an alveolar/arterial (a/A) ratio ≤ 0.23, 14 had a clinically significant response, that is they had more than 25% reduction in their oxygen index, when given Survanta [9]. In another study, only four of ten infants responded to Alveofact and, although all the infants survived, two required high frequency oscillation and another extracorporeal membrane oxygenation (ECMO). Our own experience is similar, SRT being associated with short-term improvements in oxygenation, but either high frequency oscillation or ECMO being subsequently required in a proportion of patients.

Congenital diaphragmatic hernia

The lung compliance and pressure-volume loop abnormalities in congenital diaphragmatic hernia (CDH) infants are similar to those seen in surfactant deficiency. Antenatally, amniotic fluid sampling has documented an immature lecithin:sphingomyelin ratio and absent phosphotidylglycerol in affected pregnancies. At post mortem, hyaline membranes have been noted and a decreased phospholipid fraction in the ipsilateral, compared to the contralateral, lung. Creation of a diaphragmatic hernia at 80 days postconceptional age in fetal lambs resulted not only in smaller lungs, lower total lung capacities and reduced compliance compared to controls, but a lower percentage of phosphatidylcholine and an increase in lavage proteins and surface tension. That lung model has subsequently been used to assess the efficacy of SRT in CDH. Surfactant treated animals compared to controls had better oxygenation and compliance and higher lung volumes both at 25 cm H_2O of pressure and at functional residual capacity [20]. Unfortunately those data [20] have not been confirmed in a clinical study [13]. Although SP-A levels were found to be low in infants with CDH supported by ECMO and that abnormality persisted longer than in non-CDH ECMO-treated infants, patients with CDH given four doses of bovine lung surfactant extract (Beractant) compared to control CDH infants given air did not have significantly better lung compliance or shorter duration of oxygen or ventilator dependence or hospital stay. Natural surfactant treatment, however, was suggested to have improved outcome in one small series [5], as three infants with CDH so treated prior to the first breath survived, despite a number of features which the researchers suggested had an associated high mortality: prenatal diagnosis, polyhydramnios, dilated stomach in the chest, a ventilation index greater than 1000 and a patch closure of the defect.

Severe respiratory failure

Any of the conditions discussed above may result in severe respiratory failure, in addition ARDS is now being

increasingly diagnosed in neonates. In ARDS, type II cell injury results in reduced surfactant synthesis, and there is dose-dependent protein inactivation of surfactant [16]. Surfactant dysfunction has been demonstrated in bronchoalveolar samples, not only from patients with ARDS, but those at high risk of that condition [7]. The reduction in phospholipids noted in tracheal aspirates in patients with ARDS is further decreased following the development of pneumonia or septicaemia in such patients. In animal models the response to SRT depends on the mechanism by which the ARDS is produced; SRT brings about improvements if the primary problem is surfactant deficiency, but its effect is much reduced if there is surfactant dysfunction due to protein inactivation or inhibition by antibodies.

The majority of studies involving infants with severe respiratory failure have described results from a mixed group of diagnoses, although, in one series term infants with RDS were examined who had an a/A ratio $\leq$ 0.23, 23 of 29 had a clinically significant response (a greater than 25% reduction in their oxygenation index) to a natural surfactant [9]. The effect of calf lung surfactant extract on infants with MAS or pneumonia has been investigated. Despite the infants having a mean a/A ratio of 0.09 prior to surfactant treatment, none subsequently required ECMO, died or was still oxygen dependent at 14 days of age [1]. Other groups have defined the eligibility of their patients by a requirement for ECMO. In 22 such infants, 18 whose primary diagnosis was MAS and 4 who had pneumonia, serial sampling of tracheal aspirates revealed that the levels of phospholipid and SP-A increased up to 200% in the 72 h prior to weaning and those with the greatest increase in surfactant status weaned most quickly from ECMO [4]. Natural surfactant treatment of infants receiving ECMO, who had MAS, group B sepsis with pneumonia, RDS and idiopathic pulmonary hypertension of the newborn, significantly reduced the duration of ECMO requirement [12]. The time to extubation, the duration of oxygen therapy and the age at discharge, however, did not differ between surfactant-treated infants and controls [12].

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