Seminars in Neonatology (2003) **8**, 433–440

SAUNDERS

Seminars in NEONATOLOGY

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REVIEW ARTICLE

Exogenous surfactant therapy: newer developments

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Received 1 June 2003; accepted 1 July 2003

KEYWORDS
Pulmonary surfactant;
Phospholipids;
Surfactant proteins;
Respiratory distress syndrome;
Bronchopulmonary dysplasia;
Synthetic peptide

Summary There are numerous pulmonary conditions in which qualitative or quantitative anomalies of the surfactant system have been demonstrated. In premature newborns with immature lungs, a functional deficit in surfactant is the main physiopathologic mechanism of the neonatal respiratory distress syndrome (RDS). Since the landmark pilot study of Fujiwara, published more than 20 years ago, the efficacy of exogenous surfactant for the treatment of neonatal RDS has been established by numerous controlled studies and meta-analyses. Promising results have also been reported in infants suffering from other lung disorders in which endogenous surfactant function is compromised. Enlightened by a growing insight into both the structure and function of the different surfactant components, a new generation of synthetic surfactants has been developed. Various complementary approaches have confirmed the fundamental role of the two hydrophobic proteins, SP-B and SP-C, in the surfactant system, thus opening the way to the design of analogues, either by chemical synthesis or expression in a prokaryotic system. These peptide-containing synthetic surfactant preparations are presently undergoing clinical trials, and may eventually replace the animal-derived surfactants currently used for the treatment of RDS.
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Introduction

Pulmonary surfactant, a multicomponent complex of several phospholipids, neutral lipids and specific proteins, is synthesized and secreted into alveolar spaces by type II epithelial cells.[1,2] The main functions of pulmonary surfactant are reducing the collapsing force in the alveolus, conferring mechanical stability to the alveoli, and maintaining the alveolar surface relatively free of liquid.[3] Administration of a natural animal-derived surfactant to a surfactant-deficient preterm animal or human newborn decreases the minimum pressure required to open the lung, increases the maximal lung volume, and prevents lung collapse at low pressure.[4] Phospholipids are primarily responsible for the surface-tension-lowering activity of surfactant, but other components present in animal-derived surfactants also play important roles.

Pulmonary surfactant: structure and function

Surfactant is primarily composed of phospholipids and proteins (Table 1). Most of the phospholipids consist of phosphatidylcholine (PC), and one particular PC molecule, dipalmitoyl phosphatidylcholine (DPPC), is the most prevalent component.[5] The

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doi:10.1016/S1084-2756(03)00120-9

Table 1 Composition of pulmonary surfactant (adapted from Creuwels et al.[1])

Phospholipids	85%
Saturated phosphatidylcholine (mainly DPPC)	52%
Unsaturated phosphatidylcholine	18%
Phosphatidylethanolamine	4%
Phosphatidylglycerol (PG)	8%
Phosphatidylinositol	2%
Sphingomyelin	1%
Neutral lipids and cholesterol	5%
Proteins	10%
Specific glycoproteins	
SP-A	5%
SP-D	1%
Hydrophobic proteins	
SP-B	2%
SP-C	2%

structure of DPPC is suited to form a stable monolayer generating the low surface tension required to prevent alveolar collapse at end-expiration. Phosphatidylglycerol (PG) also contributes to monolayer formation; its synthesis is restricted to type II alveolar cells, and its detection in amniotic fluid is a reliable predictor of lung maturation.[6] Phospholipids alone are far from exhibiting all the biophysical properties of pulmonary surfactant. These properties include the ability to generate low minimum surface tension on dynamic compression, to rapidly absorb from the subphase to the interface, to respread when collapse occurs after condensation, and to vary surface tension during expansion and compression at each respiratory cycle. In this respect, the contribution of low-molecular-weight SP-B and SP-C proteins to both structural organization and functional durability is essential.[7,8]

Through its life cycle, the surfactant material undergoes a series of important structural and functional transitions.[9,10] The first, lamellar bodies, the intracellular storage form of surfactant, appear within the distal epithelial cells at around 22 weeks' gestation. They become numerous and enriched with a functional surface-active material during the last weeks of a normal pregnancy. At birth, numerous lamellar bodies are actively secreted by exocytosis. In the hypophase, the thin fluid layer covering the alveolar epithelium, lamellar bodies unpack and generate tubular myelin, a transitional highly ordered lattice-like structure representing the extracellular pool of surface-active material from which the monolayer is formed. During each respiratory cycle, pauci or unilamellar small vesicles with low surface-active properties are generated from the monolayer and the tubular myelin. They represent a catabolic form destined for clearance. After birth, an efficient recycling of the alveolar surfactant pool is initiated. In term newborn rabbits, more than 90% of alveolar PC is recycled, processed by type II alveolar cells, incorporated into lamellar bodies, and eventually secreted. Tightly associated with phospholipids, the hydrophobic proteins SP-B and SP-C have an essential role in enhancing the biophysical activity of phospholipids.[8,11] These proteins promote the rapid absorption of phospholipids at the air–liquid interface, and account for the sustained low-surface-tension activity after dynamic compression.

SP-B, a 79-amino-acid peptide, has the most important surface-active permissive effect upon phospholipids.[12] Lethal respiratory failure occurs at birth in homozygous mice harbouring an SP-B gene inactivated after homologous recombination.[13] The SP-C precursor is not correctly processed, and neither lamellar bodies nor tubular myelin are detectable in type II cell cytoplasm and extracellular alveolar spaces, respectively. These features confirm the essential role of SP-B in surfactant metabolism. SP-B deficiency, inherited as an autosomal-recessive condition, has been identified in full-term newborn infants exhibiting severe and fulminant respiratory failure.[14] Although the frame-shift insertion of two nucleotides at the codon 121 is the most frequently encountered mutation (121ins2), genetic analysis of affected infants has identified more than 20 other mutations, most of them severely affecting composition, structure and function of surfactant.[15,16]

SP-C, a 35-amino-acid peptide, is made of a very large proportion of hydrophobic residues.[8,11,17] Its hydrophobic character is strengthened by two palmitoyl residues covalently linked to cysteine residues. Like SP-B, SP-C dramatically enhances the spreading of phospholipids. Whereas SP-C knocked-out animals do not manifest any respiratory symptoms at birth, SP-C-deficient adult animals develop pneumonitis and emphysema.[18] The recent characterization of a dominantly inherited mutation in the SP-C gene of siblings with interstitial lung disease suggests that either inadequate SP-C synthesis or the accumulation of an abnormal SP-C precursor may account for some forms of chronic interstitial lung disease in childhood.[19,20]

If the primary structure of both hydrophobic proteins is relatively simple, SP-A and SP-D are complex glycoproteins, built up with different domains, including a collagen-like domain close to the N-terminal extremity, a central amphipathic

Table 2 The different surfactants presently available

	Origin	Additional characteristics	Specific proteins
Modified natural surfactants	Animal lung		
CLSE			
Infasurf®)	Calf lung lavage	Chloroform/methanol extracted	SP-B/SP-C
Alveofact®	Cow lung lavage	Chloroform/methanol extracted	SP-B/SP-C
BLES			
BLES®	Cow lung lavage	Chloroform/methanol extracted	SP-B/SP-C
Surfactant TA			
Surfacten® beractant	Minced bovine lung extract	Enriched with DPPC, tripalmitoylglycerol and free fatty acids	SP-B/SP-C
Survanta®)			
Poractant			
Curosurf®)	Minced porcine lung extract	No neutral lipids (liquid-gel chromatography additional step)	SP-B/SP-C
Artificial surfactant	Synthetic preparation		
Exosurf®	DPPC + tyloxapol (6%) + hexadécanol (9%)	Artificial compounds	0

domain, and a large globular carboxy-terminal domain.[21] The collagen-like domain allows for multimerization in a triple helix, and the carboxy-terminal domain contains a calcium-dependent carbohydrate recognition region. All these features are characteristic of collectins, a subgroup of the lectin superfamily, to which the mannose-binding proteins also belong. SP-A is essential in vitro, and in collaboration with SP-B and calcium, for the structural transformation of the extracellular lamellar bodies into tubular myelin.[22] SP-A, in collaboration with SP-B and SP-C, contributes to stabilizing the phospholipid monolayer, and the addition of SP-A to a surfactant extract (containing SP-B and SP-C, but free of SP-A) improves its surface-active properties.[23] Finally, SP-A, as well as SP-D, plays a role in the innate lung defence barrier against pathogenic organisms.[24] SP-A is capable of stimulating the production of oxygen radicals by alveolar macrophages. This property, shared by SP-D, involves interactions between the protein and a specific receptor on alveolar macrophages. SP-A has also been shown to bind endotoxins, several viruses, and lipopolysaccharides of Gram-negative bacteria, enhancing the uptake of these pathogens by the alveolar macrophages. Both collectins also modulate the production of cytokines by macrophages and neutrophils. Knockout mice for each collectin have been established; the deficient animals exhibit normal respiratory behaviour at birth, but are more susceptible to infections.[25,26] Recent studies suggest that the two collectins may also regulate the functions of lymphocytes, and play a beneficial role in the modulation of the inflammatory process occurring in various pathological circumstances.[27] None of these proteins is presently a component of the natural surfactants used therapeutically. Whether SP-A- or SP-D-substituted surfactants are beneficial in the treatment of pulmonary inflammatory diseases, such as adult respiratory distress syndrome (ARDS), is a tantalizing hypothesis that might be addressed by clinical trials in the near future.

The different exogenous surfactants

Exogenous surfactants are currently classified into two families (Table 2).[28] The mammalian surfactant preparations (natural surfactant) are purified and extracted with organic solvents from either lung minces or lung lavages. Their phospholipid concentration is above 80% and all contain the low molecular hydrophobic proteins SP-B and SP-C, but not SP-A. There are several significant differences in the composition of these preparations: for instance, the porcine-minced-lung extract poractant (Curosurf®) undergoes an additional purification step that removes neutral lipid, whereas free fatty acids and DPPC are added to the bovine-minced-lung extract beractant (Survanta®). Moreover, SP-B concentration is lower in the lung-minced preparation compared with lung lavage extracts.

The entirely synthetic surfactant preparations are composed mainly of DPPC and are protein-free. Exosurf® was the most widely used synthetic surfactant, combining DPPC with a non-ionic

detergent (tyloxapol) and a spreading agent (hexadecanol). Pumactant®, another protein-devoid synthetic surfactant developed in the UK is no longer commercially available.

The immediate clinical efficacy of exogenous surfactant is demonstrated by the improvement in gas exchange following its administration. With natural preparations, the improvement is usually rapid (within a few minutes), dramatic and sustained, whereas with Exosurf®, the response is slower and less impressive. Evidence for the efficacy of either prophylactic (treatment within the first minutes after birth, regardless of respiratory status) or rescue (treatment usually after 2 h, when signs of respiratory failure are present) administration in the treatment of RDS come from overviews and meta-analysis of more than 40 trials, in which nearly 10 000 infants have been enrolled. These meta-analyses demonstrate a consistent 40% reduction in the odds of neonatal death after surfactant treatment, either natural or synthetic, and administered either a prophylactic or rescue treatment. Both types of surfactant and both treatment strategies have also resulted in a significant 30–50% reduction in the odds of pulmonary air leaks (interstitial emphysema, pneumothorax). As the increase in survival is mainly observed among extremely premature infants, the incidence of bronchopulmonary dysplasia (defined as the persistence of supplemental oxygen requirements at 28 days of life or 36 weeks of postmenstrual age) has not been significantly reduced despite the widespread use of surfactant.[29,30]

Prophylaxis, early rescue, or late administration?

Instilling surfactant before the onset of RDS has been shown to partially avoid barotrauma and vascular injury resulting from mechanical ventilation.[31] An overview of prophylactic vs rescue strategies in controlled studies demonstrates that prophylactic administration of surfactant results in a reduction in mortality (OR=0.61; 95% CI 0.48–0.77), and is associated with a reduction in the odds of pneumothorax (OR=0.62; 95% CI 0.42–0.89).[32] However, surfactant administration in the delivery room based on gestational age will result in a large number of infants being subjected to unnecessary treatment, as well as the potential side effects of endotracheal intubation (hypoxia and trauma). Indeed, with the widespread use of antenatal steroids, many very premature infants, especially those born to mothers with chorioamnionitis, have no RDS at birth. In most of the initial trials performed to evaluate the benefit of prophylaxis, the average age of administration in the rescue group was later than 4 h of life. Several trials have been conducted recently to assess the benefit of an 'early rescue' strategy (administration to symptomatic infants before 2 h of life) compared with the classic rescue treatment. The meta-analyses of these trials demonstrate that early selective surfactant administration is associated with a decreased risk of neonatal mortality (OR=0.87; 95% CI 0.77–0.99) and results in a significant reduction in the incidence of pneumothorax (OR=0.70; 95% CI 0.59–0.82).[33] A compromise between the two strategies (prophylaxis vs rescue) may be found in a careful clinical assessment of the very premature newborn stabilized in the delivery room or in the neonatal intensive care unit, with the goal of identifying infants with mature lungs. Despite nasal continuous positive airways pressure (CPAP) or endotracheal intubation along with conventional ventilation, newborns with RDS, especially the population of extremely premature infants in which the risk of developing both RDS and bronchopulmonary dysplasia remains high, usually exhibit clinical signs rapidly and may then be treated without delay, within the first 2 h of life.

Natural or synthetic surfactant?

Several randomized trials have compared the efficacy of natural surfactant with synthetic surfactant. In most of these studies, the mean FIO_2 during the 72 h after the administration of the first dose was found to be significantly lower in the population treated with natural surfactant.[34] The meta-analysis shows a significant reduction in the incidence of pneumothorax (OR=0.63; 95% CI 0.53–0.75) and mortality (OR=0.87; 95% CI 0.76–0.98) with natural surfactant.[34] The limited short-term effect of artificial surfactants is mainly explained by the absence of hydrophobic proteins in these preparations, whereas the type II cells' recycling of the exogenous phospholipids accounts for the long-term beneficial effects. As considerable attention is currently given to strategies that minimize lung injury (prophylaxis or early rescue treatment followed by rapid extubation to nasal CPAP), most institutions are predominantly using natural preparations with rapid onset of action. In this respect, infants treated with calf lung surfactant extract (Infasurf®) or poractant (Curosurf®) have a swifter improvement in oxygenation and reduced ventilatory requirements compared with infants treated with beractant (Survanta®).[35,36]

Towards a new generation of exogenous surfactant

The efficacy of natural or synthetic surfactants for the treatment of babies with RDS is well established. Experimental data and preliminary pilot studies have also provided some hope that the administration of surfactant preparations in children or adults with respiratory distress may improve gas exchange and attenuate pulmonary injury.[37] If adverse immunological reactions have not been recognized among preterm infants treated with natural surfactant extracts, concerns still remain for the administration of animal-derived proteins in more immunocompromised populations, such as children or adults with acute lung injury. This complication could be avoided with the use of synthetic surfactants containing phospholipids and chemically or genetically engineered homologous peptides.[38] Treatment with such preparations, available in unlimited amounts in contrast to animal-derived surfactants, would also completely eliminate the already very low and hypothetical risks of transmission of viral or unconventional infectious agents. It is therefore not surprising that the development of a new generation of surfactants is presently the subject of intensive research.

The most promising approach is the development of a synthetic surfactant (lucinactant, Surfaxin®) composed of DPPC, palmitoyl-oleoyl phosphatidylglycerol (POPG) and palmitic acid, combined with a synthetic peptide (Sinapultide) whose spatial structure resembles one of the amphipathic domains of SP-B.[39] These domains display an amphipathic helical structure, with hydrophobic, positively charged amino acids predominantly on one face and hydrophobic residues on the other. Various physicochemical approaches support the hypothesis that positively charged residues interact with the polar head group of phospholipids, whereas hydrophobic residues interact with their acyl side chains. KL4, a 21-residue synthetic peptide, consists of the repeated sequence KLLLL where K is lysine and L is leucine.[40] Similar to the native protein, the synthetic peptide induces molecular ordering of the phospholipid layer by contracting hydrophobic and electrostatic interactions with the phospholipids. This synthetic surfactant is more resistant to inhibition by meconium than beractant (Survanta®) or poractant (Curosurf®).[41] The administration of lucinactant (Surfaxin®) significantly improves lung volume and induces a sustained improvement in oxygenation of ventilated premature rhesus monkeys, an animal model of ARDS.[42] A pilot study demonstrated that administration of lucinactant (Surfaxin®) to premature newborns with RDS is followed by a dramatic and long-lasting improvement in oxygenation similar to that observed with natural surfactants.[43] Several randomized clinical trials are presently ongoing with the purpose of evaluating both the efficacy and safety of this surfactant, and the results are likely to be available soon.

Another synthetic surfactant composed of DPPC, POPG, palmitic acid and recombinant SP-C obtained by expression in a prokaryotic system has been developed recently.[44] This surfactant, highly effective in animal models, is currently under evaluation in the treatment of adult patients with ARDS. Other peptides have also been evaluated in experimental studies; an amphipathic alpha-helical decapeptide, whose primary structure is not related to the functional domains of SP-B, dramatically improves the surface-active properties of a mixture of phospholipids in a surfactant-deficient lung.[45] No clinical studies with this synthetic surfactant have been reported.

Do other pulmonary diseases of the newborn benefit from surfactant therapy?

Surfactant deficiency secondary to lung immaturity is not the only mechanism accounting for the occurrence of acute respiratory failure in newborns. Inactivation of surfactant by several compounds is often involved in the pathogenesis of various respiratory disorders, including meconium aspiration syndrome (MAS) pneumonia and sepsis.[46] These disorders may represent potential targets for surfactant therapy. Most of the experimental or clinical studies reported so far have been carried out with natural surfactant, mainly because surfactant proteins improve resistance of phospholipids to inactivation.

Meconium aspiration syndrome

Perinatal aspiration of meconium secondary to intrapartum asphyxia is a cause of severe respiratory failure in full- or post-term infants. The physiopathologic mechanisms of hypoxaemia include airway obstructions, chemical pneumonitis, persistent pulmonary hypertension of the newborn with right-to-left extra-pulmonary shunting, and surfactant dysfunction. Surfactant is inhibited by meconium in vitro and in vivo. The hydrophobic fraction of meconium is the most potent inhibitor. In rabbits with experimental MAS, early treatment with a natural surfactant prevents lung injury and

improves ventilation efficiency.[47] Several groups have reported encouraging results in pilot studies with natural surfactant administered to infants with severe MAS.[48,49] The meta-analysis of two recent randomized, controlled trials confirms the benefit of natural surfactant in MAS; the administration of several doses of a natural preparation improves oxygenation and reduces the need for extracorporeal membrane oxygenation.[50–52] Bronchoalveolar lavage with dilute surfactant seems to be a promising approach for the treatment of severe MAS. Assessed recently in an animal model of acute lung injury,[53] this method was also evaluated in the treatment of severe MAS in both an open and a small randomized, controlled pilot study.[54,55] In the latter trial, 15 infants with severe MAS were submitted to a series of bronchoalveolar lavages with dilute lucinactant (Surfaxin®). A trend towards a more rapid improvement in oxygenation and a shorter duration of mechanical ventilation was observed in the treated group. Based on these results, a phase 3 clinical trial is presently underway in the USA to assess both the efficacy and safety of bronchoalveolar lavage with dilute lucinactant (Surfaxin®) in severe MAS.

Neonatal bacterial pneumonia

Neonatal bacterial pneumonia may affect surfactant functions by various mechanisms. Inactivation by plasma-derived proteins and blood components present in the alveolar spaces (haemoglobin, fibrinogen, immunoglobulins, etc.), induction of bacterial secretion of phospholipases, and injury to the alveolar epithelium compromising the synthesis and the secretion of surfactant may all play a role. Chorioamnionitis also accounts for a large percentage of premature births; surfactant inactivation and deficiency may therefore co-exist. Moreover, some of the surfactant components may play a role in the lung defences against infection, and surfactant deficiency may worsen the infectious process. Indeed, early administration of a high dose of a natural surfactant (Curosurf®) to newborn rabbits has been shown to prevent intrapulmonary proliferation of group B streptococci.[56] In a recent retrospective review of a large series of preterm and term infants with respiratory failure associated with group B streptococcal sepsis, improved oxygenation and decreased ventilatory requirements were observed after administration of natural surfactant.[57] However, there is presently insufficient evidence that surfactant treatment improves the long-term outcome of septic newborns with respiratory failure.

Conclusion

Although it is well established that surfactant therapy improves survival of very premature infants, concern remains over the high incidence of bronchopulmonary dysplasia. A way of reducing lung injury in this vulnerable population may be found in the use of nasal CPAP, either prophylactically in the delivery room to avoid intubation and lung injury, or immediately after early administration of surfactant.[58,59] Several clinical trials addressing this important question are presently underway. Whether conventional surfactant substitution or bronchoalveolar lavage with dilute surfactant improve long-term outcome of newborns with severe MAS is another important issue presently under investigation. Finally, it is likely that surfactant preparations with native or analogous peptides will soon be available. Such preparations, designed to confer high resistance to inactivation by manipulating the ratio of phospholipids/hydrophobic proteins, may find new clinical indications in the near future.

Practice points

- Surfactant is the most researched drug to reduce mortality related to RDS, but it has not been shown to reduce the incidence of bronchopulmonary dysplasia.
- At present, natural surfactants seem to have an advantage in terms of quicker action and reduced pneumothorax.
- Surfactant given prophylactically seems to have an advantage compared with its use as a rescue treatment.

Research directions

- Peptide-containing synthetic surfactants may become a suitable alternative to animal-derived surfactant currently used for treatment of RDS.
- Expanded use of surfactants in conditions other than hyaline membrane disease is being explored.
- Stricter criteria regarding re-dosing of surfactant need to be evaluated.

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