Conferences and Reviews

Pulmonary Surfactant Therapy

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Surfactant replacement therapy is now an integral part of the care of neonates since several clinical trials of natural surfactant extracts and synthetic preparations have shown efficacy in the treatment of infants with hyaline membrane disease. In these studies, early treatment with exogenous surfactant substantially reduced mortality and the incidence of air leak, although it did not appear to reduce the incidence of other complications, in particular bronchopulmonary dysplasia. Early reports of exogenous surfactant therapy in patients with the adult respiratory distress syndrome, although promising, remain limited in number. More research is needed to improve on current modes of therapy and to investigate the possible role of surfactant in other lung diseases of both newborns and adults.

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The possible role of surface forces in the lungs was first considered in 1929 by the Swiss scientist Kurt von Neergaard.[1] Two and a half decades later, Pattle[2] and Clements[3] independently demonstrated the existence of surface-active material in the alveoli of animal lungs. Soon after, in 1959, Avery and Mead established the relationship between this surface-active material, lung surfactant, and hyaline membrane disease of human neonates.[4] Since then, a great deal of effort has been devoted to studying the biologic properties of lung surfactant and its potential as a human therapy. The first report of the beneficial use of surfactant therapy in neonates with the respiratory distress syndrome (RDS) was published in 1980.[5] Several ensuing trials demonstrated the efficacy of exogenous surfactant in reducing the mortality and morbidity attributable to RDS. These results led the United States Food and Drug Administration (FDA) to approve the use of surfactants in neonates in 1990.

In this review, we summarize some biologic aspects of pulmonary surfactant, outline conclusions drawn from clinical trials using surfactant preparations in neonates, and discuss some of the questions that remain unanswered.*

Surfactant Composition

Lung surfactant is a complex lipoprotein assembled and secreted into the alveolar spaces by alveolar epithelial type II cells. Its composition, being fairly constant among mammalian species,[6] consists of about 90% lipids and 10% proteins. The main lipid fraction is the saturated lecithin dipalmitoyl phosphatidylcholine (DPPC). Negatively charged phospholipids are present in high proportion (10% to 15%), as is free cholesterol (about 10%). A variety of other phospholipids and neutral lipids make up the remainder of the lipids. Three lipid-associated apolipoproteins have been isolated from lung surfactant and designated SP-A, SP-B, and SP-C.[7] Two of these, SP-B and SP-C, are small hydrophobic proteins that co-isolate with lipids. SP-A, on the other hand, more easily dissociates from lipids and can be solubilized in water.[8] A fourth protein, SP-D, has recently been purified from lung lavage and does not appear to directly interact with lipids.[9] SP-D bears striking structural homology to SP-A, and along with mannose-binding protein and serum conglutinin, belongs to the newly described "collectin" family.[10] This complex lipoprotein has unique functional properties.

Biologic Properties of Lung Surfactant

The primary function of lung surfactant is to lower surface tension at the air-water interface of the lung alveoli, thereby stabilizing lung volume at low transpulmonary pressure. Adsorption of DPPC by itself to the liquid surface is poor,[11] but it is greatly enhanced by surfactant apoproteins.[12]

Attention has recently been directed to the immune properties of surfactant. Apoproteins SP-A and SP-D appear to have specific immune properties. Both proteins bind to bacteria[13,14]; SP-A enhances the

*See also the editorial by R. J. Mason, MD, "Surfactant Replacement Therapy—Room for Improvement," on pages 74-76 of this issue.

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ABBREVIATIONS USED IN TEXT

CPHT = colfosceril palmitate, hexadecanol, and tyloxapol
DPPC = dipalmitoyl phosphatidylcholine
FDA = United States Food and Drug Administration
RDS = respiratory distress syndrome

phagocytosis of bacteria[13] and viruses[15] and promotes the chemotaxis of phagocytic cells.[16]

Other properties of surfactant may include inhibiting pulmonary edema formation[17] and enhancing fluid dispersal[18] and ciliary transport in small airways.[19]

Surfactant Metabolism

The synthesis of lung surfactant appears to be restricted to alveolar epithelial type II cells, although nonciliated bronchiolar cells have been shown in several species to make surfactant apoproteins.[20] Once assembled, the components of surfactant are stored in secretory organelles, lamellar bodies, before their secretion into the alveolar liquid subphase where they undergo structural transformations that lead to the formation of the surface layer (Figure 1). Labeling studies show that surfactant is in a state of continuous flux and that type II cells are capable of regulated endocytosis and recycling of the various surfactant components.[21]

Surfactant Replacement Therapy

Before it was approved by the FDA for human use, exogenous surfactant underwent extensive testing in a great number of well-designed, carefully controlled, and properly randomized clinical studies that have set a standard of scientific excellence and productive collaboration in the neonatal community.

We will briefly describe the preparations that were tested (Table 1). Surfactant-TA (Surfacten, Tokoyo Tanabe, Tokyo, Japan) and beractant (Survanta, Abbott Laboratories, Chicago, Illinois) are made from minced lungs and modified by the addition of phospholipids and fatty acids. Infasurf (Forrest Laboratories, New York, NY) and calf lung surfactant extract are made from calf lung lavage extracts, and SF-RI 1 (Alveofact, Boehringer, Ingelheim, Germany) is from cow lung lavage extracts. Curosurf (Chiesi Pharmaceuticals, Parma, Italy) is derived from minced pig lung extracts. Amniotic fluid surfactant is the only human preparation

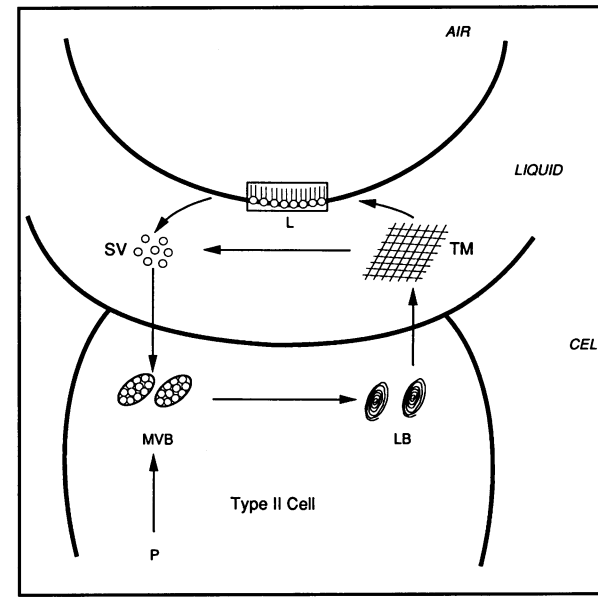

Figure 1.—A simplified overview of surfactant turnover is shown: Type II cells synthesize and assemble precursors **(P)** of surfactant into multivesicular bodies **(MVB)** and secrete lamellar body **(LB)** contents into the alveolar liquid lining where they undergo structural transformations: tubular myelin **(TM)** feeds the surface layer **(L)** and small vesicles **(SV)** are recycled into type II cell multivesicular bodies.

characterized and tested. The two synthetic preparations that were the most extensively tested are the artificial lung-expanding compound (ALEC, Britannia Pharmaceuticals, United Kingdom) and colfosceril palmitate, hexadecanol, and tyloxapol (CPHT; Exosurf Neonatal, Burroughs Wellcome Company, Research Triangle Park, North Carolina), but others were or are being developed.

Analyzing in detail each of the trials is beyond the scope of this review, and our intent is to summarize the conclusions that can be drawn from published results.

Clinical Trials of Exogenous Surfactant in Neonatal Respiratory Distress Syndrome

Trials that followed the report by Fujiwara and colleagues[5] help answer the following questions:

TABLE 1.—*Surfactant Preparations*

Surfactant Type	*Material*	*Proteins*
Bovine	Modified minced lung extracts (surfactant TA [Surfacten])	SP-B, SP-C
Bovine	Modified minced lung extracts (beractant [Survanta])	SP-B, SP-C
Bovine	Calf lung lavage extracts (CLSE, Infasurf)	SP-B, SP-C
Bovine	Cow lung lavage extracts (SF-RI 1 [Alveofact])	SP-B, SP-C
Porcine	Minced lung extracts (Curosurf)	SP-B, SP-C
Human	Human amniotic fluid extract	SP-A, SP-B, SP-C
Synthetic	DPPC-PG (artificial lung-expanding compound)	None
Synthetic	DPPC, CPHT (Exosurf Neonatal)	None

CPHT-colfosceril palmitate, hexadecanol, and tyloxapol; DPPC-PG = dipalmitoylphosphatidylcholine-phosphatidylglycerol; SP-A = surfactant apoprotein A; SP-B = surfactant apoprotein B; SP-C = surfactant apoprotein C

TABLE 2.—*Prophylactic Trials of Surfactant Preparations*

Trial	Preparation	Dosage	Infants: Age, wk (Weight, grams)	Infants: No.	Outcome
Enhorning, et al, 1985[24]	CLSE	Single	< 30	72	↓Death, ↓IVH
Kwong et al, 1985[25]	CLSE	Single	24-28	27	No difference
Kendig et al, 1988[26]	CLSE	Single	25-29	65	↓Pneumothorax
Merritt et al, 1986[27]	Human	Multiple	24-29	60	↓Death, ↓pneumothorax
Soll et al, 1990[28]	Beractant	Single	24-30 (750-1,250)	156	↓Pneumothorax, ↑NEC
Hoekstra et al, 1991[29]	Beractant	Multiple	23-29 (600-1,250)	430	↓Death, ↓pneumothorax
Ten Centre Study Group, 1987[30]	ALEC	Multiple	25-29	328	↓Death
Morley et al, 1988[31]	ALEC	Multiple	< 34	341	↓Death, ↓BPD, ↓IVH in < 30 wk
Phibbs et al, 1991[32]	CPHT	Single	(700-1,350)	74	No difference
Bose et al, 1990[33]	CPHT	Single	(700-1,350)	385	↓PIE
Stevenson et al, 1992[34]	CPHT	Single	(500-699)	215	↓Pneumothorax, ↑pulmonary hemorrhage
Corbet et al, 1991[35]	CPHT	Single	(700-1,100)	446	↓Death, ↓pneumothorax

ALEC = artificial lung-expanding compound; BPD = bronchopulmonary dysplasia; CLSE = calf lung surfactant extract; CPHT = colfosceril palmitate, hexadecanol, and tyloxapol; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PIE = pulmonary interstitial emphysema

• *Can the prophylactic administration of exogenous surfactant prevent RDS and its complications?*

The prophylactic administration of surfactant aims at instituting surfactant in the airway as soon as the infant is delivered and before breathing has even begun. Possible advantages of this approach are indicated by experiments in prematurely delivered animals that showed that exogenous materials distribute better when instilled in a partially or totally fluid-filled airway[22] and that, in the absence of surfactant, damage to the airway occurs early (in the first hour) after the initiation of mechanical ventilation.[23] Results from trials testing different preparations (Table 2)[24-35] were subjected to meta-analyses.[36,37]

From these analyses, it was concluded that the prophylactic administration of surfactant decreases neonatal mortality and the incidence of air leak. Although these effects did not reach statistical significance in all trials, they appeared consistent across populations and with all surfactant preparations tested. Despite initial hopes to the contrary, however, the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, and other complications of prematurity remained essentially unchanged. Because systematic prophylactic treatment of neonates at risk for RDS would result in a large number of them being subjected to unnecessary treatment, investigators were led to test exogenous surfactant therapy in infants with established RDS.

• *Can surfactant therapy decrease the incidence and severity of RDS and its complications?*

In the "rescue" mode of surfactant therapy (also referred to as "treatment"), infants are treated after the diagnosis of RDS has been established by clinical and radiologic criteria. Several investigators tested this approach in randomized trials (Table 3).[38-49] Again, meta-analyses of the results showed a decrease in mortality and air leak similar to that found in prophylactic trials.[36,37] Moreover, there was again little or no effect of surfactant therapy on sequelae associated with RDS. In particular, there was no notable effect on the incidence of bronchopulmonary dysplasia in survivors, although there was variability in the results among different-weight groups within and between studies. Direct comparative trials of the two approaches (prophylactic versus rescue) were also done.

• *Is prophylactic better or worse than rescue therapy in decreasing mortality and morbidity associated with RDS?*

Despite published results from five comparative human trials addressing this question (Table 4),[50-54] the answer remains uncertain. Two trials found no significant differences between the two modes of administration.[53,54] One study found increased oxygen requirement at 28 days after birth in the prophylactic group in contrast with decreased oxygen requirement at 36 weeks postconception in the rescue group.[50] On the contrary, a pronounced decrease in mortality and air leak was found in the group born at or before 26 weeks' gestation that received prophylactic therapy.[51] It was also found that prophylactic therapy decreased mortality when compared with rescue administration in the population of infants (29 to 32 weeks' gestation) studied.[52]

Although prophylactic treatment may lead to a delay in stabilizing a neonate, rescue treatment can be given as soon as the diagnosis of RDS is established, earlier than at the times tested in trials. The OSIRIS trial found a decreased incidence of "death or oxygen dependence at the expected date of delivery" and of air leak in infants treated early, before 2 hours of age, when compared with those treated later,[55] and a recent report from Japan found a decreased incidence of bronchopulmonary dysplasia in infants treated before 30 minutes of age compared with those treated at 6 hours of age.[56]

• *Do additional doses of surfactant provide further benefits to patients?*

Two trials showed benefit from repeated doses,[57,58] although the effects on mortality and the incidence of air

TABLE 3.—*Surfactant "Rescue" Trials*

Trial	Preparation	Dosage	Infant Features: Weight, grams	No.	Lung Physiology	Hours After Birth	Outcome
Gitlin et al, 1987[38]	Surfactant TA	Single	1,000-1,500	41	Fio_2 >0.4	<8	↓Pneumothorax
Raju et al, 1987[39]	Surfactant TA	Single	751-1,750	30	Fio_2 >0.5	<6	↓Death and ↓pneumothorax;↑PDA
Fujiwara et al, 1990[40]	Surfactant TA	Single	750-1,750	100	Fio_2 >0.4		↓Pneumothorax, ↓IVH
Hallman et al, 1985[41]	Human	Multiple	<1,500	45	Fio_2>0.6	<10	↓Pneumothorax
Lang et al, 1990[42]	Human	Multiple	24-32*; 1,500	59	Fio_2 >0.8	<12	↓Pneumothorax
Horbar et al, 1989[43]	Beractant	Single	750-1,750	159	Fio_2 >0.4	3-6	↓Pneumothorax
Horbar et al, 1990[44]	Beractant	Single	750-1,750	106	Fio_2 >0.4	3-6	↑IVH
Liechty et al, 1991[45]	Beractant	Multiple	600-1,750	798	Fio_2 >0.4	<8	↓Death, ↓pneumothorax
Gortner et al, 1990[46]	SF-RI 1	Multiple	25-30*	69		<1	No difference
European Collaborative Group, 1988[47]	Porcine	Single	700-2,000	146	Fio_2 >0.6	2-15	↓Death, ↓pneumothorax
Phibbs et al, 1991[32]	CPHT	Single	>650	104	Fio_2 >0.4-0.5	4-24	No difference
Long et al, 1991[48]	CPHT	Multiple	700-1,350	419	a/A <0.22	2-24	↓Death, ↓pneumothorax and PIE
Long et al, 1991[49]	CPHT	Multiple	>1,250	1,237	a/A <0.22	2-24	↓Death; ↓BPD and pneumothorax; ↓IVH and ↓PDA

a/A = arterial-alveolar Po_2 ratio; BPD = bronchopulmonary dysplasia; CPHT = colfosceril palmitate, hexadecanol, and tyloxapol; Fio_2 = fraction of inspired oxygen; IVH = intraventricular hemorrhage; PDA = patent ductus arteriosus; PIE = pulmonary interstitial emphysema

*Age in weeks.

leak reached significance only in the larger study.[58] It was reported in one abstract that infants treated with multiple doses of the synthetic surfactant CPHT had reduced neonatal mortality and a reduced need for oxygen and ventilatory support.[59] A later report of a large, albeit not placebo-controlled or blinded, international study indicated that more than two doses of CPHT appear to provide little, if any, additional benefit.[55]

• *Is surfactant instillation safe?*

The most common adverse reaction seen after the tracheal instillation of surfactant was a transient deterioration of gas exchange, which responded well to and often could be prevented by an adjustment of the ventilator settings.[60,61] Airway obstruction occurred with an incidence of about 3 patients per 1,000 in trials testing the use of CPHT.[62] The incidence of such events when using other surfactant preparations has not been precisely ascertained.

An increase in the incidence of pulmonary hemorrhage was reported in a trial examining the effects of prophylactic CPHT in infants weighing 500 to 699 grams at birth.[34] On review of retrospective[63,64] and autopsy analyses,[65] however, the relative risk for pulmonary hemorrhage with any surfactant therapy is estimated to be no greater than 1.5.[64]

A report of an increase in the incidence of intraventricular hemorrhage in treated infants[44] was not confirmed by other trials and appears to have been an isolated incidence.[66]

Administering human or animal-derived extracts to infants raised concerns over the infectious risk posed to patients and the potential for their sensitization to the protein fraction contained in the preparations. Isolated reports of increased incidence of bacterial sepsis did not reach statistical significance,[29] and to date no other report of serious infectious complication has appeared. Two studies failed to detect immune complexes[67] or circulating antibodies[68] in the serum of infants who received natural preparations, but one showed a suppression of the mitogen-induced proliferation of cord blood lymphocytes by the natural surfactant SF-RI 1.[68]

Although the long-term follow-up of infants treated with surfactants has been limited both in the number of subjects and the duration, it has not shown adverse developmental effects of treatment.[69-74] Increased survival of infants with disabilities might be expected, however, and several studies indicated such a trend.[69,71,72]

• *Are any of the available preparations better than the others?*

There is currently one published trial comparing the efficacy of CPHT and beractant administered in a rescue mode.[75] Although there were small differences favoring the use of beractant in the effects on ventilatory settings needed to maintain comparable early gas exchange in the two groups, there was no observed difference in the mortality or incidence of any of the complications between the two groups. Studies comparing different preparations with those already tested are ongoing, but results have yet to be published.

Surfactant Therapy for Other Pulmonary Diseases

The main measurable effect of exogenous surfactant on lung mechanics of infants with RDS is an increase in functional residual capacity, possibly through stabilizing partially ventilated alveolar units and recruiting previ-

TABLE 4.—*Rescue Versus Prophylaxis Comparative Trials*

Trial	Preparation	Dosage	Infants			Outcome
			Age, wk	No.	Lung Physiology	
Dunn et al, 1991[50]	CLSE	Multiple	< 30	182	<6 hr*	↓Pneumothorax and ↓BPD in treatment group
Kendig et al, 1991[51]	CLSE	Multiple	24-29	479	Fio_2 >0.4	↓Death and ↓pneumothorax in prophylaxis group
Kattwinkel et al, 1993[52]	CLSE	Multiple	29-32	1,398	Fio_2 >0.3	↓Death in prophylaxis group
Merritt et al, 1991[53]	Human	Multiple	24-29	203	Fio_2 >0.5; 2-12 hr*	No difference
Egberts et al, 1993[54]	Porcine	Multiple	26-29	147	Fio_2 >0.6; 6-24 hr*	No difference

BPD = bronchopulmonary dysplasia, CLSE = calf lung surfactant extract, Fio_2 = fraction of inspired oxygen

*Hours refer to time after birth.

ously nonventilated ones.[76] Tidal volume and lung compliance, however, remain unchanged or decrease slightly.[76]

Diseases of the lungs other than RDS may also be ameliorated with surfactant therapy. Studies in animals have suggested benefits of using exogenous surfactant in a variety of conditions, including pneumonia (bacterial,[77] aspiration[78]), asthma,[79] and after lung transplantation.[80] In humans, exogenous surfactant improved lung mechanics and gas exchange in neonates with the meconium aspiration syndrome[81] and in infants with respiratory failure requiring extracorporeal membrane oxygenation.[82] The use of surfactant replacement therapy was also tested in adults and children with adult RDS. Preliminary reports have been encouraging,[83,84] but controlled trials are clearly called for.

Remaining Questions, Future Prospects

Despite the success of surfactant replacement therapy in neonates with RDS, several questions pertaining to its use in clinical practice remain unanswered. In most trials a small fraction of the infants had little or no response to therapy.[85,86] The proportion of these "nonresponders" varied with the population studied, but was as high as 24% in one study.[86] Subsequent analyses suggested that the presence of prenatal asphyxia increases the risk of a poor response,[87] as do those of large patent ductus arteriosus and high fluid intake.[88] A number of other factors could also contribute to limit the response to surfactant therapy:

- The dose of surfactant administered may be insufficient. The amount of surfactant administered in trials varied from 60 to 200 mg of phospholipids per kilogram. These doses were chosen largely on the basis of theoretical considerations, but little experimental work has been done to establish the correct dosing and administration regimen. Two trials specifically addressed the effects of the initial dosage. One found that administering 120 mg per kg of surfactant TA was more effective than half that dose.[89] Another showed that 67.5 mg per kg of CPHT was more effective than half and as effective as double that dose.[90]
- The administration of surfactant may be ineffective because surfactant fails to reach the respiratory units or it is inactivated in situ, for instance by extravasated serum proteins.[91] The distribution of exogenous surfactant in the lungs may also be affected by its mode of delivery, that is, bolus versus slow instillation.[92] Aerosol delivery of surfactants is being tested in the treatment of patients with adult RDS,[84] but it has the serious disadvantage that, with current methods, administering an adequate dose takes hours or even days.
- Ventilation strategies may affect the response to therapy.[88] Preparations with different physical characteristics are expected to affect the patient's lung mechanics differently,[76] and ventilator settings may need to be adjusted accordingly, as has been shown in animals.[93]
- Surfactant therapy is only a palliative treatment, limited in time, and patients ultimately depend on an effective endogenous surfactant production for full recovery. This point is illustrated by the report of a patient who died of neonatal RDS refractory to repeated exogenous surfactant administration and who was found at autopsy to lack the normal production of surfactant apoprotein B because of a genetic defect.[94,95] Other genetic abnormalities are likely to be discovered that alter the normal production or functional properties of surfactant components.
- The administration of antenatal steroids is an important element in determining outcome in infants, as shown by several investigators. One report showed recently that infants whose mothers had received steroids antenatally had lower requirements for surfactant treatment or ventilator support and a lower incidence of intraventricular hemorrhage.[96] A retrospective analysis of trials using beractant showed that the prenatal administration of steroids reduced neonatal mortality to the same extent as did the postnatal administration of surfactant and that steroids and surfactant together have additive effects.[97] These observations confirm the results of an earlier analysis[98] and of animal experiments showing structural maturation of the lung after prenatal steroid therapy.[99]

Finally, several laboratories are working to improve currently available preparations. The use of recombinant and synthetic peptides that attempt to mimic the proper-

ties of hydrophobic surfactant-associated proteins is a promising avenue of approach.[100-102]

Conclusions

In early 1995, have the closing lines in the fascinating story of surfactant biology been written? To the contrary, several important questions remain about pulmonary surfactant, its biologic processes, and its role in lung homeostasis and disease states. Furthermore, investigation of other modes of therapy, such as partial[103] or total[104] liquid ventilation, could lead to alternative treatments for special situations in which exogenous surfactant may prove not to be optimal therapy. Although we should not underestimate the achievements of recent years in this field, it is clear that much more research will be needed to complete our understanding of the lung surfactant system and to enable us to manipulate it to best advantage for patients with pulmonary diseases.

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