Drugs 38 (4): 591-611, 1989
0012-6667/89/0010-0591/$10.50/0

DRUG03 263a

Exogenous Surfactant Treatments for Neonatal Respiratory Distress Syndrome and their Potential Role in the Adult Respiratory Distress Syndrome

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Summary

Exogenous surfactant therapy has been recognised as an approach to alleviating the surfactant-deficient state for 3 decades. Natural and lipid-extracted surfactants derived from amniotic fluid, lung lavage, or lung homogenates are being used in worldwide clinical trials in premature infants. These studies are demonstrating a generally favourable influence on lung function by improving oxygenation and reducing the risk for pneumothorax and pulmonary interstitial emphysema. In some studies, reduction in death and the occurrence of bronchopulmonary dysplasia have been found. Numerous questions are unresolved and pharmacokinetic data are limited in preterm infants. Artificial surfactants are similarly under evaluation but current data demonstrate less overall effect.

Adult respiratory distress syndrome has also been treated with exogenous surfactants. Although complex in terms of multiple initiating factors and in terms of high permeability of surfactant inhibitors, further studies are under way to determine the ideal methods of administration to enhance distribution and to monitor surfactant function in vivo.

Surfactants are surface-active physicochemical agents that reduce the attractive forces exerted on the surface molecules of a liquid by molecules in the liquid phase beneath the surface. The surface tension-reducing properties of surfactants compel the liquid to assume the shape having the least area. They behave as detergent-like agents in their function, and in biological systems they serve as a critical 'membrane' between biological junctions such as the air-cell membrane layers within the lung. This review focuses on new developments in pulmonary surfactant biology and critically analyses the evidence that neonatal and adult respiratory syndromes may be successfully treated by the use of exogenous surfactants. Recent advances and emerging clinical trial data are establishing the efficacy of exogenous surfactant therapy in reducing morbidity and mortality in neonatal respiratory distress syndrome associated with surfactant deficiency and immaturity, while studies are under way to determine disorders characterised by alterations in pulmonary surfactant biophysical activity such as occurs in the adult respiratory distress syndrome.

Pulmonary surfactants have existed as potentially efficacious drugs for nearly a decade. In the past 10 years the variety of agents being evaluated for their ability to replenish the surfactant-deficient state of neonatal respiratory distress syndrome (RDS) has increased dramatically. In addition, efforts are presently under way to develop this promising therapy for the treatment of the heterogeneous condition termed adult respiratory distress syndrome (ARDS). Indeed, surfactant research as a whole has been expanding, for it was not until the early 1980s that the existence of low molecular weight 'proteolipid'-like proteins in lipid extracts of minced lung or lavage was appreciated. The fundamental role of these proteins in contributing to the rapid film formation of the phospholipid-protein complexes at the alveolar hypophase-air boundary has now been established.

1. Surfactant Deficiency

1.1 Historical Perspective

Von Neergaard (1929) showed 60 years ago that much larger pressures were required to expand an air-filled lung than to distend a lung filled with fluid if the surface tension effect at the air-liquid boundary was eliminated. 26 years later, Pattle (1955) demonstrated that pulmonary oedema fluid had bubbles with great stability, and suggested that surfactant was an 'anti-oedema' factor. Clements (1956) reported on the surface tension-lowering capabilities of lung extracts using a Wilhelmy plate dipped into a Langmuir trough and measured surface activity of lung extracts, and predicted the amount of this material required to stabilise the lung's air-filled spaces. Following the description by Avery and Mead (1959) of the reduced activity of surface active material in the lungs of infants dying with hyaline membrane disease, Klaus et al. (1961) suggested that dipalmitoylphosphatidylcholine (DPPC) was the principal surface active constituent of lung surfactant. This discovery led Chu et al. (1967), and in Canada Robillard et al. (1964), to treat premature infants with lecithin by aerosol, but the results were clearly unimpressive. Emerging data on the composition of surfactant during human gestation permitted the development of antenatal tests performed on amniotic fluid. Gluck et al. (1971) measured the ratio of highly saturated phophatidylcholine to sphingomyelin throughout the last trimester of pregnancy and established that if this ratio (using a semiquantitative acetone precipitation to isolate disaturated lecithin) was greater than 2, the chance of developing respiratory distress syndrome was small. Hallman and Gluck (1976) described phosphatidylglycerol, the second most abundant phospholipid in surfactant, and established that its absence closely correlated with the development of respiratory distress syndrome. The relationships between the acidic phospholipids, phosphatidylinositol and phosphatidylglycerol, have also been defined. During the last trimester phophatidylinositol content increases in the surfactant isolated from amniotic fluid until about 34 to 35 weeks' gestation, and then decreases while there is an increase in phosphatidylglycerol. This is due to changes in substrate availability (myoinositol) and in the regulation of cytidine diphosphatidylglycerol synthetase activity with preferential synthesis of phosphatidylglycerol in the last weeks of gestation (Hallman et al. 1986b). Meas-

urements of these phospholipid constituents in amniotic fluid form the basis of the antenatal tests of lung maturity commonly used in perinatal medicine.

Surfactant-associated proteins were described in lung lavage from dogs by King et al. (1973). They reported that surfactant contained some 10% protein, along with serum protein contaminants. Two major water soluble surfactant-specific proteins [molecular weights of 35,000 daltons (35kD) and 11kD] were found; however, not until lipid extracts of surfactant (devoid of the 35kD protein) were found to bestow surfactant activity were the hydrophobic low molecular weight surfactant proteins described and characterised (Takahashi & Fujiwara 1986). These latter proteolipid-like proteins of about 18kD (SP B) and 3.5 to 9kD (SP C) have been noted to have no immunological cross-reactivity with the larger glycoprotein and, when recombined with phospholipids such as dipalmatidylphosphatidylcholine and phosphatidylglycerol in the proper stoichiometry, absorb rapidly to the liquid-air interphase and lower surface tension to near 0 mN/m. A cooperative relationship between the low molecular weight proteins (SP B and SP C) and the 35kD protein (SP A) has been described by Hawgood et al. (1987) in terms of rapid surface adsorption.

Morphological studies have shown that surfactant is secreted as lamellar bodies from the type II alveolar cell. Once secreted they are transformed to tubular myelin (wherein the larger protein is associated) and then undergo both a recycling (binding to and internalisation) within the type II cell, a small fraction undergoing macrophage degradation.

Based on some of the above information, and the notable failure of phospholipids alone to improve lung function in premature infants, Enhorning and Robertson (1972) first reported that a 'complete' surfactant derived from centrifuged lung lavage of adult rabbits could restore lung expansion in premature rabbit fetuses. Adams et al. (1978) demonstrated that intratracheal instillation of natural surfactant reversed the clinical and histological features of atelectasis in premature lambs. Fujiwara et al. (1980) extended these observations in human infants, their initial report in 1980 describing the effects of a lipid-extracted surfactant in reversing respiratory failure.

1.2 Composition of Natural and Extracted Surfactants

The composition of human amniotic fluid surfactant is dependent on the methods by which it is obtained, separated, and analysed. Natural human surfactant obtained from human amniotic fluid at term and isolated by sucrose density ultracentrifugation is quite similar to that obtained from lung lavage of adults. The relationship of the low molecular weight proteins to the 35kD protein and various phopholipids is being established, but the process is complicated by changes in the composition of the surfactant during purification. Animal-based surfactants are prepared by a variety of lipid extraction techniques, which isolate phospholipids, neutral lipids, cholesterol, and low molecular weight proteins using organic solvents and/or gel/liquid column chromatography, resuspended in saline to form large multi- or univesicular liposomes. Animal surfactants have been prepared from lung mince or lung lavage of young or mature cows or swine (Notter et al. 1985; Possmayer et al. 1984; Taeusch et al. 1986). Some surfactant preparations contain additional phospholipids and fatty acids (i.e., 'Surfactant TA'), while others are only extracted lipids (i.e., 'CLSE' also called 'Infasurf'). Porcine surfactant ('Curosurf') is void of neutral lipids, which have been removed by column chromatography (Berggren et al. 1985). While natural surfactants contain both 35kD and low molecular weight surfactant proteins (about 5% protein by weight), the extracted phospholipids contain variable amounts (about 1%) [Notter et al. 1987] of the lower molecular weight proteins (see table I).

1.3 Artificial Surfactants

Artificial surfactant preparations containing only the synthetic phospholipid DPPC and phosphatidylglycerol moieties in a fixed ratio of 7 : 3 have

Table I. Composition of human surfactant

	Human amniotic fluid surfactant[a,b]	Adult human lung surfactant[a,c]
Phosphatidylcholine	77.6[c]	80.5 ± 1.4
disaturated	51.2 ± 2.9	44.7[d]
other	-	35.8
Phosphatidylglycerol	7.6 ± 1.7	9.1 ± 0.4
Phosphatidylinositol	6.4 ± 0.7	2.6 ± 0.4
Phosphatidylethanolamine	5.0 ± 0.4	2.3 ± 0.8
Phosphatidylserine	0.4 ± 0.4	0.9 ± 0.2
Sphingomyelin	1.6 ± 0.5	2.7 ± 0.4
Others	1.4 ± 0.2	1.9 ± 0.1
Protein	5.4 ± 2.0[e]	2.0
Neutral lipids	9.4 ± 2.4	Not measured

a Data are expressed as percentage by weight of the total composition. Phospholipids are expressed using inorganic phosphorus (Pi) determination with conversion of μmol of Pi to mg of phospholipid, assuming 31g Pi per mol Pi and that Pi comprises 4% by weight of total phospholipid.

b Data from Hallman et al. (1983).

c Data from Shelley et al. (1977).

d Determination of disaturated phosphatidylcholine was made using a modification of the method reported by Mason et al. (1976).

e Protein concentration was determined by the method of Pierce and Suelter (1977).

been used extensively in England as a dry powder or as a liquid suspension (Milner et al. 1984; Morley et al. 1981; Ten Centre Study Group 1987). The results of these large clinical trials are encouraging; however, there has not been universal success using these agents (Wilkinson et al. 1985). For example, infants treated with this mixture ('Artificial Lung Expanding Compound', 'ALEC') did not have improved oxygenation or the need for lower ventilator pressures characteristic of infants treated with natural surfactants, but a more delayed improvement suggested that it enhanced substrate for *de novo* surfactant synthesis (Jobe & Ikegami 1987). Halliday et al. (1984) reported that a mixture of DPPC and serum high-density lipoprotein in a 10 : 1 ratio instilled at birth to prevent respiratory distress syndrome did not have a beneficial effect in alleviating respiratory failure or in improving outcome. More recently a synthetic surfactant containing DPPC, hexadecanol, tyloxapol, and sodium chloride ('Exosurf') has been introduced for clinical testing in the US and Canada (Long & Sanders 1988) after tests in rabbit fetuses (Tooley et al. 1987) and immature lambs (Durand et al. 1985) showed that it modestly improved pulmonary mechanics in these animal models. To date the results of clinical trials of this synthetic surfactant in premature infants have not been published.

2. Surfactant Therapy

2.1 Required Physiological Effects

In order for a surfactant preparation to be effective in pulmonary mechanics, it must effectively lower surface tension on dynamic compression in a Langmuir trough and Wilhelmy balance or pulsating bubble surfactometer; be adsorbed rapidly from the subphase to the air-liquid interface (Notter 1988), and be respread after maximum compression. As noted by early workers, it must also have the capacity to vary surface tension during dynamic activity (inspiration and expiration). These biophysical properties are translated into the physiological changes characterised by improved dynamic compliance (at normal transpulmonary pressures), increased alveolar stability during expiration, decreased transvascular leakage of proteins and water into the alveolus, and decreased atelectasis. Because surfactants are subject to 'inhibition' of their biophysical properties and thus their potential physiological effects (Fuchimukai et al. 1987), pharmaceutical surfactant preparations should also ideally be 'resistant' to inhibition and not interact or bind with other drugs or proteins within the lung that might alter pulmonary function or clearance, enhance lung inflammation, or induce pulmonary haemorrhage.

Although a number of immature animal models have been used to evaluate the desired biophysical properties, none entirely mimic neonatal respiratory distress syndrome. Most of the animal experiments have been of short duration (usually less than 12 hours), and the fetal animals have been ventilated differently than are infants in the intensive care nursery. These studies have not consid-

ered factors other than lung function, such as cerebral blood flow, shunting through the ductus arteriosus etc., which complicate the clinical management of human infants. Studies in fetal lambs have shown that the *in vivo* performance of various surfactant preparations is not related to their *in vitro* performance. This suggests that short term animal models do not mimic clinical respiratory distress syndrome and that the performance of various surfactants in fetal lambs is different from their performance in infants, or that measures of efficacy in the studies of human infants are not equivalent to those in the animal studies. This observation stresses the essential need to evaluate the pharmacological effects on surfactant in preterm human newborns, rather than in animal models.

2.2 Toxicology and Immunological Evaluation

Because preterm infants are extremely vulnerable to lung injury, and because ill effects of drugs may not present themselves for years (for example, the link between diethylstilboestrol exposure and the later development of clear cell adenocarcinoma), it is critical that surfactant preparations or any of their components be non-toxic in the dosages administered to human infants. Because the therapeutic index of the surfactant preparation might be quite low in preterm infants with immature pulmonary, cardiovascular, hepatic, renal, and immunological function, it is essential that toxicological evaluation extend beyond the usual rodent and non-rodent species testing to include fetal animals near term which have respiratory distress syndrome. Furthermore, it is essential that long term follow-up studies of pulmonary function, somatic growth and development be conducted on these animals. Testing the toxicology of a mixture of 90% DPPC and 10% dipalmitoylphosphatidylglycerol given intravenously in mice and rats has resulted in lethal dose values in 50% of animals (LD_{50}) of 415 mg/kg and 353 mg/kg, respectively (Obladen et al. 1979). These researchers found that the trachea, bronchi, and lung parenchyma remained normal up to 24 hours after instillation of 500mg DPPC/phosphatidylglycerol mixtures. No evidence of inflammation, necrosis, ulceration or other mucosal damage was detected in the upper airways.

Unfortunately, there are no precedents for evaluating the toxic effects of drugs administered via the intratracheal route in preterm infants, taking into account the varying degree of surfactant deficiency. Recent randomised, controlled clinical trials have indicated that a single dose of surfactant is ineffective in alleviating ventilatory failure in almost 50% of infants beyond 20 to 24 hours after administration (Horbar et al. 1988; Kendig et al. 1988; Soll et al. 1988), while another study reported success with a single dose of 'Curosurf'. The most appropriate toxicological testing must evaluate the potential effects of surfactants in subjects who may have altered mechanisms of drug or biological clearance. It must further be recognised that infants with respiratory distress syndrome may have other conditions that complicate the surfactant-deficient state (e.g. pneumonia, pulmonary oedema from 'leaky' capillaries or from increased pulmonary blood flow caused by the ductus arteriosus) which may be altered by surfactant instillation into the airways.

Of further concern is the potential for immunological sensitisation to surfactant proteins when heterologous surfactants are administered. The lung is a major site of antigen-antibody reactivity, thus the potential for immune complex formation or injury must be considered. Immune complex formation has been reported both in infants receiving surfactant and in those receiving conventional treatment, and although the immune complex has not been shown to cause harm, this finding raises the possibility of immunological toxicity. Hull and Whitsett (1988) evaluated sera from infants receiving a phospholipid-fatty acid preparation, 'Surfactant TA', and were unable to detect circulating antisurfactant antibodies to the low molecular weight proteins postnatally and up to 6 months after birth.

The evaluations only examined sera of infants treated with a single dose of a bovine surfactant for free circulating antibodies and failed to test for immune complex formation or report evidence of complement activation. Merritt et al. (1988) ex-

amined infants for surfactant-antisurfactant immune complexes and reported, as did Strayer et al. (1986) in an earlier study, that immune complexes were detectable in infants receiving human surfactant and in most control infants. There was no evidence of complement depletion, renal disease, or cutaneous rash attributable to an immunological reaction in treated infants during the first year of life. Furthermore, Dunn et al. (1988) did not identify milk allergies or other 'allergic' symptoms in infants receiving bovine surfactant. *In vitro* testing suggests that the low molecular weight surfactants are immunogenic in several species, and that surfactant function may be substantially altered by contact with antisurfactant antibodies (Strayer et al. 1986). Since phospholipids may themselves be immunogenic in some conditions (anticardiolipin antibodies found in patients with lupus erythematosus, for example) it must not be assumed that repeated doses of phospholipids via the intratracheal route are necessarily innocuous. Unfortunately, no studies have been published demonstrating lack of toxicity or immunogenicity among the heterologous surfactants when used in multiple doses to treat premature infants. Certainly such data will undoubtedly be forthcoming if these agents are to be approved for non-investigational, routine use in premature infants.

2.3 Pharmacological Effects and Dosage

As described above, biophysical properties that correlate to the physiological properties of natural surfactant at 37°C [surface adsorption, low minimum surface tension (< 10 mN/m), and stability of the film formed by the surfactant monolayer] appear to be essential for exogenous surfactant to function *in vivo*. Testing of surfactants for their 'susceptibility' to known inhibitors of function (serum proteins, bilirubin, haemoglobin) should also be performed. However, the concentrations used and the conditions of exposure in these bioassays are usually quite arbitrary and may not replicate the conditions within the lungs of premature infants. *In vivo* testing must also be performed in animal models in which pulmonary surfactant is deficient (e.g. neonatal respiratory distress syndrome) or in which surfactant is inhibited, depleted, or both, as in adult respiratory distress syndrome.

Most *in vivo* evaluations have been performed in the fetal rabbit, fetal lamb, or baboon at about 0.8 to 0.9 term gestation, which is analogous to human gestation of 30 to 36 weeks, where the incidence of respiratory distress syndrome is 20 to 60%. The limitations of animal models for mimicking this condition have been discussed by de Lemos and Kuehl (1987) and the Food and Drug Administration of the United States (Goldenthal 1968). Their analyses suggest that fetal rabbits (27 days' gestation) and baboons (135 to 140 days' gestation) have proven to be useful as animal models of respiratory distress syndrome and for *in vivo* testing of surfactants. Animal models of lung lavage such as those described extensively by Bermel et al. (1984) or those resulting from prolonged exposure to high levels of oxygen are also useful. Although surfactant that is efficacious in treating neonatal respiratory distress syndrome may be useful in adults, this must not necessarily be assumed. Physiological and pharmacological effects must be tested in the multiple models of adult respiratory distress syndrome and in clinical trials. Measurements of dynamic lung compliance, blood gases, alveolar/arterial oxygen tension ratios, lung water estimates, epithelial leaks of vascular proteins or other inhibitors in airway fluids, airway fluid inflammatory cell numbers and mediators, chest radiographs, and ventilatory support indices over periods of hours are essential to establish clinical efficacy and safety. Lung histology from animal studies which demonstrate resolution of atelectasis, lack of epithelial necrosis, desquamation, or inflammation after surfactant treatment are reassuring. Many experiments with larger animal models have also examined other complicating conditions frequently encountered in the preterm infant, including the effect of the patent ductus arteriosus (PDA). Studies to date (Heldt et al. 1989; Shimada et al. 1986; Vidyasagar & Shimade 1987) do not support an earlier observation by Clyman et al. (1982) that surfactant treatment markedly

worsens left-to-right PDA shunting. While pharmacological studies have been performed for the surfactants currently being evaluated in clinical trials, few reports evaluating multiple-dose therapy after worsening of respiratory distress syndrome have been reported. Current published data demonstrating reversal of respiratory distress syndrome in animal models and in clinical trials exist for 'Surfactant TA', human surfactant, 'Curosurf', 'CLSE', bovine surfactant extract, and 'ALEC', while 'Exosurf' has been shown to partially improve lung function in the fetal lamb and rabbit (tables II and III). Dosage of surfactant preparations has varied in reported studies.

The amount of surfactant given should restore the surfactant pool within the alveoli and type II pneumocytes. Since neonates have a surfactant pool size that is 5- to 10-fold greater than adults, effective doses may be smaller than those needed to treat adult respiratory distress syndrome. Initial dosage was based on fetal rabbit data, which suggested that surfactant in amounts greater than 40 mg/kg (Metcalfe et al. 1982) did not improve lung compliance or stability. Ikegami et al. (1982) found that the pressure-volume relationships of the lungs of preterm lambs were maximally improved at doses of 53 mg/kg, whereas minimal surface tensions and stability indices of alveolar washes were obtained at a dose of 65 mg/kg. In initial clinical trials doses ranged from 25mg of dry surfactant (7 : 3 mixture of DPPC : phosphatidylglycerol) to as much as 200mg of porcine surfactant instilled via endotracheal tubes (Robertson et al. 1986). The dose of 'ALEC' was found to acutely increase the lecithin/sphingomyelin ratio in tracheal aspirates; however, by 20 hours after treatment this ratio had returned to pretreatment values, suggesting clearance or degradation of the instilled preparation (Wilkinson et al. 1985). Hallman et al. (1986a) detected phosphatidylglycerol for 24 hours in tracheal aspirates of infants receiving human surfactant at birth, indicating potential differences in the clearance of this acidic phospholipid from the lung. In infants treated with human surfactant (60 mg/kg or at least 60mg), these workers found absence of phosphatidylglycerol in the airway fluid of infants prior to human surfactant treatment, but a 5- to 10-fold increase in the disaturated phosphatidylcholine/sphingomyelin ratio for 2 to 3 days. Sequential determinations of phosphatidylglycerol content in tracheal aspirates suggest that the half-life of this instilled phospholipid was 30 hours. These data parallel the clinical severity of respiratory distress syndrome, as judged by the ventilatory index, where an intitial response is followed by a slow deterioration over 20 to 30 hours. Retreatment with 60 mg/kg of surfactant prompts a recovery phase in most infants. Up to 4 doses were given in trials of human surfactant with similar responses. These findings have also been substantiated in animal experiments where repeated doses also attenuated the tendency to relapse (Walther et al. 1985).

Heterologous surfactant preparations have been administered in higher doses. Both 'CLSE' and 'Surfactant TA' were administered at approximately 100 mg/kg in the reported clinical trials, while 'Curosurf' was instilled at doses of 200 mg/kg (Noack et al. 1987). Konishi et al. (1986) compared an initial dose of 120 mg/kg to 60 mg/kg using 'Surfactant TA'. Their data suggest that the higher dose resulted in greater clinical improvement during the 72 hours after treatment, and resulted in less bronchopulmonary dysplasia and intracranial haemorrhages. A recent report of a clinical trial by Kendig et al. (1988) using single-dose 'CLSE' treatment has been less encouraging. The severity of the respiratory distress syndrome was reduced for 24 hours and there was no improvement in mortality or reduction in bronchopulmonary dysplasia. Current clinical trials are evaluating multidose therapy and early observations have indicated that this results in an improved and more sustained response.

The route of administration has usually been by direct instillation of this slightly viscous suspension into the endotracheal tube, although suspensions of surfactant 'powder' have been aerosolised and ventilated into the airway or instilled into the hypopharynx. During administration the infant is usually placed in the right and left lateral decubitus positions while being mechanically or manually

Table II. Summary of post-ventilatory (rescue) trials of surfactant (S) [adapted from Merritt & Hallman 1988a, with permission]

Type of surfactant	Reference	No. of patients		Treatment criteria	Outcome
		S	controls		
Supplemented bovine homogenate ('Surfactant TA')	Fujiwara et al. (1980)	10		RDS	↑ paO_2; ↓ $paCO_2$; ↓ FiO_2; ↓ A/aO_2; 9/10 PDA
	Fujiwara (1981)	19	3 comparison infants	RDS	↑ pO_2/FiO_2; ↓ FiO_2; ↑ PDA
	Fujiwara et al. (1984)	20	10	RDS	↓ A/aO_2; ↓ MAP; chest radiograph improvement
	Fujiwara (1984)	37	5	RDS	↓ A/aO_2; ↓ FiO_2; chest radiograph improvement; ↑ PDA
	Raju et al. (1987)	17	13	MAP ⩾ 8; a/AO_2 ⩽ 0.25; ⩽ 6h	↓ FiO_2; ↓ A/a gradient; ↓ air leaks; ↑ PDA
	Gitlin et al. (1987)	18	23	⩾ 1000g; < 1500 IMV; < 8h; FiO_2 ⩾ 0.4	↓ days ⩾ 0.4; ↓ O_2 days
Supplemented bovine homogenate ('Survanta')	Horbar et al. (1989)	78	81	750-1750g	↓ FiO_2; ↓ vent. support at 72 hours; ↓ air leaks; no effect on mortality
Bovine lung lavage extract	Smyth et al. (1981)	3		Severe RDS	↑ paO_2; ↓ FiO_2 chest radiograph improvement
	Smyth et al. (1983)	6		Not listed	↑ a/A gradient; 24-hour effect
Porcine ('CK')	Kobayashi et al. (1981)	1		RDS	Chest radiograph improvement; ↑ paO_2/FiO_2; ↓ $paCO_2$
	Ohta et al. (1981)	1		RDS	'Improvement'
	Nohara et al. (1983)	6		RDS	↑ paO_2 in 4/6; chest radiograph improvement
'Curosurf'	Berggren et al. (1984)	4		Severe RDS	↑ paO_2; ↓ $paCO_2$; ↓ air leaks
	Collaborative European Multicenter Study Group (1988)	77	69	Severe RDS; 700-2000g	↓ death and/or BPD; ↓ air leaks
	Halliday et al. (1988)	55		Severe RDS; 28.8 wks GA; 1200 ± 337g	↓ air leaks; mortality 16%; BPD 27%
Human amniotic fluid ('Human Surf')	Hallman et al. (1983)	6	6	< 10h; < 29 wks; L/S ⩽ 2.0; no PG	↑ paO_2; ↓ $paCO_2$; chest radiograph improvement
	Hallman (1985)	25	28	< 10 h; < 1500g; severe RDS; L/S < 2.0; no PG	↓ death or BPD; ↓ air leaks; ↓ days FiO_2 > 0.3 at 30 days
	Lang et al. (1988)	10	14	25-32 wks; severe RDS; 5.6h mean treatment time	↑ paO_2; ↓ FiO_2; ↑ a/AO_2; ↓ MAP
Human amniotic fluid surfactant	Jianwu et al. (1988)	1		2.25kg; severe RDS treated at age 29h	↑ paO_2; ↓ MAP; infant survived

Table II. Contd

Type of surfactant	Reference	No. of patients		Treatment criteria	Outcome
		S	controls		
Synthetic phospholipids DPPC 7:PG:3 ('ALEC')	Milner et al. (1983)	10		RDS	No effect
	Wilkinson et al. (1985)	12		⩽ 32 wks; RDS	No effect; ↑ L/S in tracheal fluid
	Weintraub et al. (1985)	22		RDS; ⩾ 20cm PIP; FiO_2 > 0.6	↓ $paCO_2$; ↓ PIP; 8/22 died
DPPC: hexadecanol: tyloxapol ('Exosurf')	Phibbs (1988)	45	40	> 650g; 4-24h; radiographic RDS; FiO_2 ⩾ 0.4-0.5; MAP 7 if < 1250g; MAP 8 if > 1250g	Slight ↓ FiO_2; slight ↓ MAP at 24 hours; no difference in deaths at 1 month

Abbreviations and symbols: RDS = respiratory distress syndrome; PG = phosphatidylglycerol; $paO_2/paCO_2$ = partial pressure of oxygen/carbon dioxide in arterial blood; FiO_2 = fractional inspiratory oxygen concentration; PDA = patent ductus arteriosus; MAP = mean airway pressure; IMV = intermittent mandatory ventilation; BPD = bronchopulmonary dysplasia; GA = gestational age; L/S = lecithin/sphingomyelin ratio; a/AO_2 = arterial-alveolar oxygen tension ratio; PIP = peak inspiratory pressure; ↑ signifies an increase; ↓ signifies a decrease.

ventilated. These manipulations usually result in a rapid improvement in arterial oxygen. The techniques of administration, however, have not been rigorously controlled and chest radiographs have revealed unilateral deposition of surfactant with clearing of atelectasis (Edwards et al. 1985; Wood et al. 1987), while the reticulogranular pattern characteristic of respiratory distress syndrome is apparent on the contralateral side. Because tiny premature infants may be difficult to intubate, it is essential that only an experienced neonatologist administer surfactant and manipulate ventilatory settings after administration. Figure 1 illustrates the usual radiological resolution of respiratory distress syndrome following treatment with human surfactant. Mechanical ventilator usage and initial settings vary from one intensive care nursery to another, but our experience suggests that initial ventilator settings of 30 to 40 breaths/min, positive inspiratory pressures of 20 to 25cm H_2O (1.96-2.45 kPa), positive end-expiratory pressures of 4 to 5cm H_2O (0.39-0.49 kPa), and inspiratory durations of 0.5 to 0.8 seconds are optimal for most infants of less than 30 weeks' gestation. After treatment we usually reduce the fraction of inspiratory oxygen concentration (FiO_2), followed by reductions in peak pressures and ventilator rates. The FiO_2 can usually be reduced to less than 0.3 to 0.4 in 6 hours, and an accelerated course of 'weaning' from assisted ventilation can be accomplished.

2.4 Clinical Efficacy of Surfactant Preparations

In clinical trials surfactant preparations have been evaluated in comparison with conventionally ventilated infants from 23 to 24 weeks' gestation to 32 to 34 weeks. Most study designs have not required that premature infants treated with surfactant have evidence of surfactant deficiency (i.e. reduced pool size or immature surfactant composition), and a variety of 'placebo' agents have been administered, including saline which has been shown to worsen lung function in animal studies (Egan et al. 1983). Studies of efficacy have included trial designs evaluating both the post-ventilatory administration of surfactant in varying doses to reverse ventilatory failure (rescue), and prophylactic administration before or nearly simultaneously with the first breath. These trials have compared the ventilatory support and oxygen needs of infants

Table III. Summary of prophylactic surfactant (S) treatment (adapted from Merritt & Hallman 1988a, with permission)

Type of surfactant	Reference	No. of patients		Treatment criteria	Outcome
		S	controls		
Supplemented bovine homogenate ('Survanta')	Soll et al. (1988)	79	81	750-1250g; intubated 4-37 minutes after birth	Chest radiograph improved for 24h; 750-999g better responders; no improvement a/AO_2; no improvement in clinical status in 7-28 days
	Horbar et al. (1988)	38	46	750-1750g	↑ a/AO_2; ↓ MAP; ↑ IVH in European study
Bovine lung lavage extract	Enhorning et al. (1985)	39	33	≤ 30 wks	↓ death; ↓ IVH; ↓ air leaks; more male infants in the controls; no sex difference in RDS 17 males/18 females
Calf lung surfactant extract	Shapiro et al. (1985)	16	16	25-29 wks	Transient ↓ in RDS severity
	Kendig et al. (1988)	34	31	25-29 wks	↓ severity RDS for 24 hours; ↓ air leaks; no effect on mortality
'Infasurf'	Kwong et al. (1985)	14	13	24-28 wks	↓ RDS severity at 48 hours; ↓ FiO_2; ↓ ventilatory support
	Kwong & Egan (1988)	315		23-29 wks	↓ Death; historical 'controls'
	Bloom (1988)	43 'Infasurf'; 13 human amniotic fluid surfactant	30	24-31 wks	↓ death; ↓ PIE; no concurrent or randomised controls
Bovine surfactant ('SR-RI1')	Gortner (1988)	34	35	< 30 wks GA; $FiO_2 > 0.4$; PIP 22.25	↑ Survival with no BPD; ↓ FiO_2
Human amniotic fluid ('Human Surf')	Merritt et al. (1986)	31	29	24-29 wks; L/S ≤ 2.0; no PG	↓ death; ↓ BPD; ↓ air leaks
Synthetic phospholipids DPPC 7:PG:3 ('ALEC')	Morley et al. (1981)	22	33	≤ 34 wks	↓ Death; more males in controls
	Wilkinson et al. (1985)	16	16	≤ 32 wks with resuscitation	No effect
	Milner et al. (1984)	10	6	≤ 34 wks needing intubation	No effect
	Ten Centre Study Group (1987)	159	149	25-29 wks	↓ mortality; ↓ hours ventilated; ↓ brain parenchymal haemorrhage
DPPC + high density lipoproteins ('Exosurf') hexadecanol: tyloxapol	Halliday et al. (1984)	49	51	25-33 wks	No effect
	Phibbs (1988)	29	31	700-1350g; < 34 wks GA; no anomalies; no erythroblastosis	↓ FiO_2 for 48h; ↓ PIP at 24-48h; no effect on survival

Table III. Contd

Type of surfactant	Reference	No. of patients		Treatment criteria	Outcome
		S	controls		
Comparison of prophylactic and rescue treatment with surfactant					
Calf lung surfactant extract	Shapiro et al. (1988)	78	81	24-29 wks GA; prophylactic RDS; MAP $\geq$ 7 or $FiO_2 \geq 0.4$ for rescue	Rescue treatment equivalent to prophylactic treatment in outcome
Human amniotic fluid ('Human Surf')	Merritt & Hallman (1988b)	23	23	Twins 24-29 wks GA; rescue twin with $FiO_2 > 0.5$; MAP > 7; L/S < 2.0; no PG	Rescue treatment better than prophylactic in terms of survival with no BPD

Abbreviations and symbols: see table II; IVH = intraventricular haemorrhage; PIE = pulmonary interstitial emphysema.

with respiratory distress syndrome at various postnatal ages (1, 6, 12, 24 hours, etc.), and the frequency of complications of the syndrome, including mortality. Figures 2, 3 and 4 compare clinical response to 3 surfactant preparations given either as prophylactic or rescue treatment. Mean airway pressures dropped from 8cm H_2O (0.78 kPa) in infants treated with human surfactant over the initial 12 to 24 hours, while in 'CLSE'-treated infants mean airway pressures dropped from 7 to 6cm H_2O (0.69-0.59 kPa) at 12 and 24 hours. However, as these infants received only a single dose of 'CLSE', the beneficial effect on mean airway pressure was reversed over the next 24 hours. Over the initial 24 hours, the ventilatory index was similar in infants treated with human surfactant and 'CLSE'. It is of interest that the placebo-treated infants in the 'CLSE' trial were less ill (as evidenced by lower ventilatory indices) than the control infants in the human surfactant trial. In contrast, infants receiving 'Curosurf' after developing severe respiratory distress syndrome (mean age 9.0 hours; range ≤ -15 hours) had a lesser response to rescue, with a decrease to about 50% 12 to 24 hours after randomisation. Improvement in the arterial-alveolar oxygen tension ratios (a/AO_2) is quite similar between infants treated with human surfactant and with 'Curosurf'. In this trial 'Curosurf' was given only once at a dose of 200 mg/kg. That these measures of ventilatory support and oxygen requirement are quite similar after treatment with different surfactants and a range of doses suggests that respiratory distress syndrome can only be moderately reduced, without total resolution of the disease.

Most studies have demonstrated that surfactant treatment improves a/A oxygen tension ratio, and allows the use of lower mean airway pressures. The duration of mechanical ventilation is reduced and most studies have also demonstrated a decreased incidence of pulmonary air leak, and little change in other frequently encountered morbidities in premature infants, with the exception of patent ductus arteriosus. Pulmonary mechanics should be improved when surface tension forces within the lung have been reduced by the administration of surfactant. Davis et al. (1988) found that the administration of 'CLSE' improved pulmonary mechanics during spontaneous breathing, but not during ventilator-assisted breaths. Tidal volume increased by 32%, minute ventilation by 38%, dynamic compliance by 29%, and inspiratory flow rates by 54% immediately after surfactant treatment. We have found variably improved dynamic compliance in some infants receiving intermittent mandatory ventilation following surfactant treatment as a 'rescue' between 6 and 18 hours after birth (fig. 5). This is probably due to the overdistension of the lungs caused by mechanical ventilation, which masks the mechanical improvement bestowed by

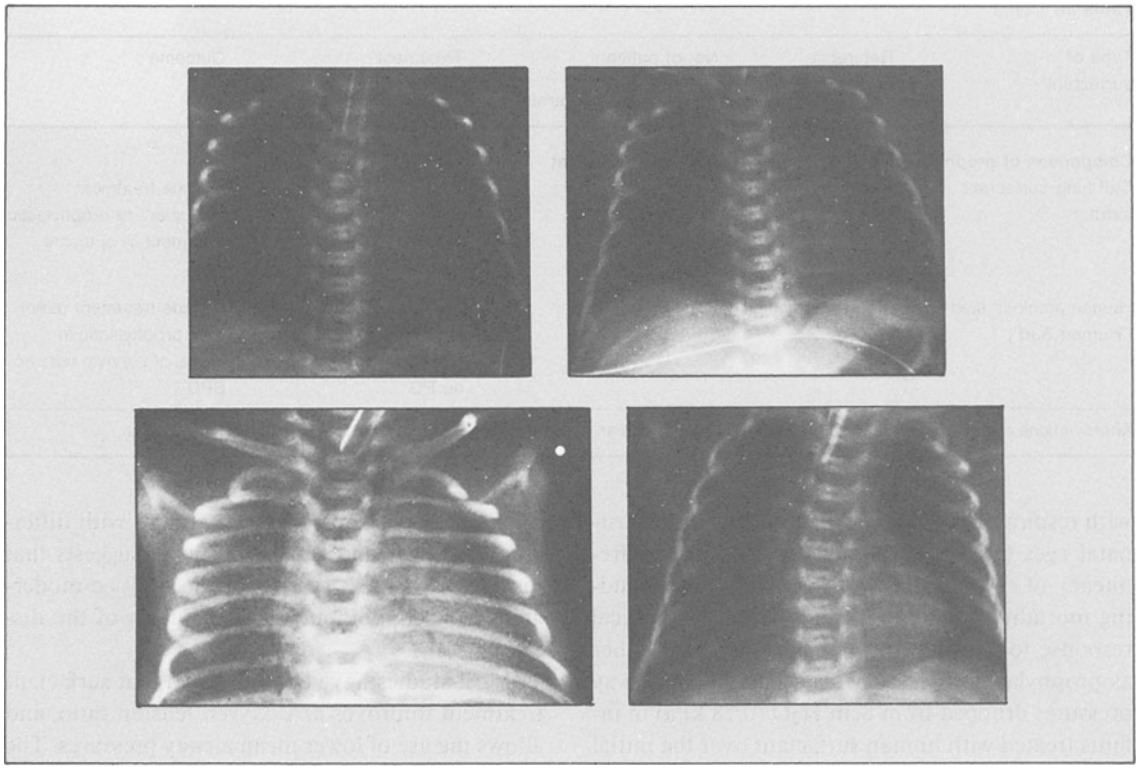

Fig. 1. Chest radiographs obtained on twin infants delivered by caesarean section at 28 weeks' gestation. The upper 2 radiographs are at 1 and 16 hours after the birth of the first-born infant girl, weighing 1200g. The upper left panel, 1 hour after receiving human surfactant at birth, shows normal lung inflation, absence of reticulogranular pattern and a normal heart size. 16 hours after birth the lungs are essentially unchanged, with an enlarged heart compatible with a patent ductus arteriosus.

In contrast, the lower radiographs are of the second-born twin (1330g) who received placebo at birth and has developed radiographic features of respiratory distress syndrome. This infant was treated with human surfactant 2 hours after birth. 15 hours later the chest radiographs show clearing of reticulogranular pattern and absence of air bronchograms. The radiopaque 'dot' over the left shoulder of the second twin is a marker of that twin's radiographs.

surfactant treatment. Measurement of pulmonary mechanics may help to determine strategies of assisted ventilation after surfactant replacement therapy.

Because chronic lung disease frequently follows treatment for respiratory distress syndrome, effective surfactant therapy should reduce the occurrence of bronchopulmonary dysplasia and its severity. This has been demonstrated in the studies of Merritt et al. (1986) with human surfactant and the European Multicentre Study, using 'Curosurf' (Collaborative European Multicentre Study Group 1988). McCord et al. (1988) recently reported that 'Curosurf' treatment was also associated with a reduction in the frequency of intraventricular haemorrhage and pneumothorax compared with control infants. Extension of intraventricular haemorrhage occurred more frequently in control infants; however, no differences were noted in the frequency of the most severe forms of intraventricular haemorrhage between 'Curosurf'-treated and control infants despite significant reductions in oxygen and mechanical ventilation requirements. While preterm infants are susceptible to a variety of other

problems, including immature gastrointestinal function and reduced myocardial and renal function, and are at increased risk for infection, effective surfactant therapy alone, while reducing complications and mortality specific to respiratory distress syndrome, may not improve overall mortality.

2.5 Follow-Up Studies

Pharmaceutical agents used in infants and children must not only effectively treat disease, they must be free from adverse effects that might contribute to mortality and/or morbidity during the remainder of the infant's life. Since surfactant treatment is being used in a group of infants with a higher than normal incidence of actual and potential handicaps, it is essential to compare the outcomes in infants treated with various surfactant agents with those of control infants (achieved in randomised, controlled, clinical trials) receiving similar neonatal intensive care. Halliday et al. (1986) found that while a synthetic surfactant composed of dipalmitoylphosphatidylcholine and high-density lipoprotein had no beneficial effects in altering the course of respiratory distress syndrome,

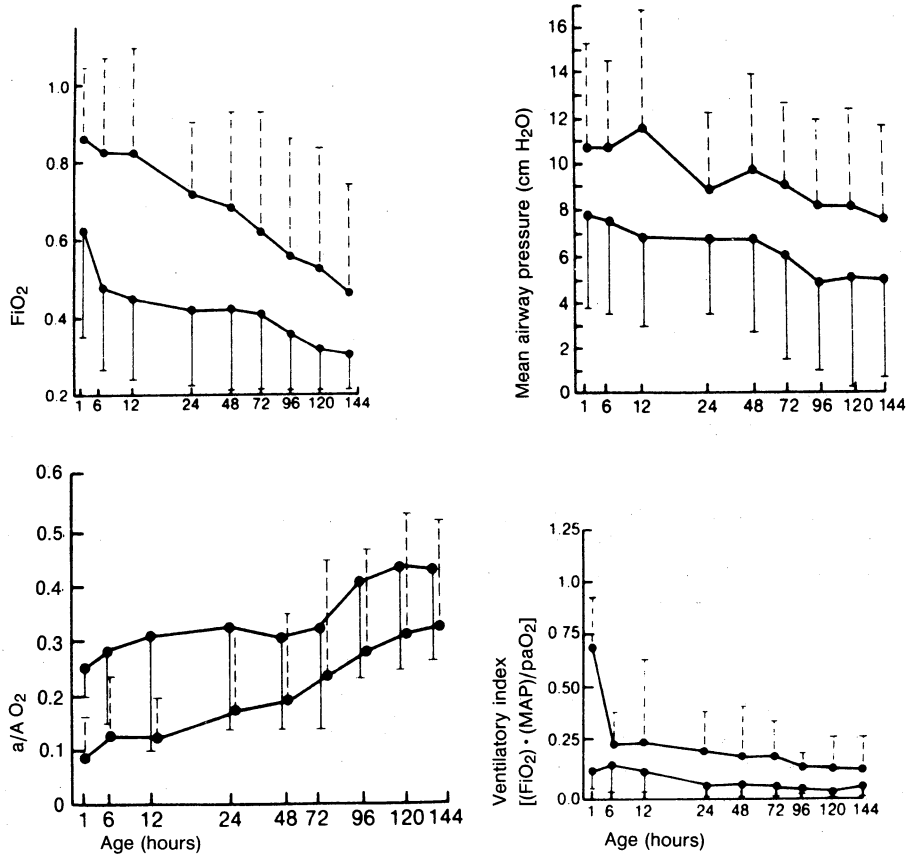

Fig. 2. Data for neonates given human surfactant (60 mg/kg) as prophylaxis. Surfactant-treated infants are represented by solid circles with solid line as standard deviation bars, while control infants are represented by solid circles with broken standard deviation bars. At all time points the magnitude of supplemental oxygen and mean airway pressures were less in surfactant-treated infants. Accordingly the a/AO_2 and ventilatory index are improved in recipients of surfactant. In this study multidose therapy was given as needed (up to 4 doses) [reproduced from Merritt et al. (1986) with permission].

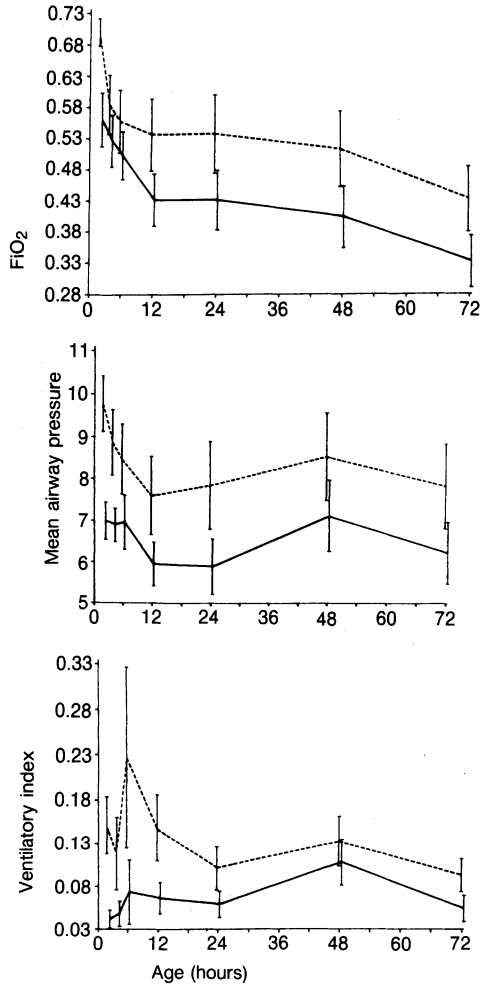

Fig. 3. Data for infants treated with CLSE (100 mg/kg). Infants treated at birth with 'human surfactant' had similar declines in FiO_2 over the initial 12 hours (to 45 and 43%, respectively) [reproduced from Kendig et al. 1988, with permission].

no evidence of harm could be found when these 39 infants were prospectively followed for growth and development. Furthermore, wheezing, skin rashes or food intolerance did not occur more frequently in the infants treated with surfactant than in controls. Dunn et al. (1987) have published a report of a 2-year follow-up study of infants treated with bovine extract surfactant. Handicaps were evident in both control and treated infants, but more infants in the surfactant-treated group had an adverse neurodevelopmental outcome, which the authors attribute to chance. Vaucher et al. (1988) found that among infants born between 1983 and 1986, neurodevelopmental scores at 2 years of age were similar between surfactant-treated infants and controls although the surfactant-treated infants had a reduced incidence of bronchopulmonary dysplasia. Dunn et al. (1988) have suggested that surfactant therapy appears to save some infants from death, but that they survive to lead a handicapped existence. This sobering observation suggests that careful monitoring of the overall effects of treatment with these agents will be necessary in the years to come.

2.6 Drug Interactions

To date no drug interactions with surfactant preparations have been identified. Because premature infants with respiratory distress syndrome frequently receive numerous drugs, it is essential that drug interaction studies be performed before these agents are registered.

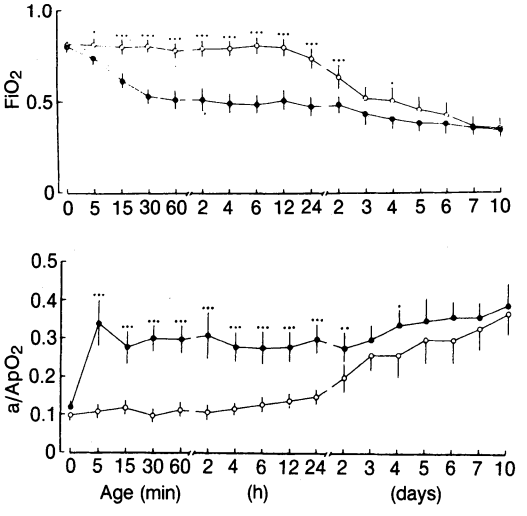

Fig. 4. Data for infants treated with post-ventilatory 'Curosurf' treatment (200 mg/kg). The decrease in FiO_2 was less (to approximately 52%) among 'rescued' infants receiving 'Curosurf' than in those treated at birth with 'human surfactant' or 'Curosurf' (reproduced from Collaborative European Multicentre Study Group 1988, with permission).

Among infants exhibiting symptoms of respiratory distress at birth, 5 to 10% will have congenital pneumonia. Surfactants instilled into the lungs of preterm infants may alter the inflammatory response elicited in the host's response to these infections. Using experimental models of congenital pneumonia with infection caused by *Streptococcus agalactiae* type Ia in 28-day fetal rabbits exposed to an FiO_2 of 0.6, Sherman et al. (1988) have shown that surfactant therapy ('Surfactant TA', 'Curosurf', phospholipid mixtures of DPPC : phosphatidylglycerol 7 : 3, human surfactant, or 'CLSE') does not significantly affect proliferation of intrapulmonary streptococci. 'Exosurf', however, was shown to impair intrapulmonary proliferation of these organisms when compared with other surfactants. Infection with *Escherichia coli,* however, was inhibited by 'Exosurf' and 'Curosurf', while 'CLSE', human surfactant, and 'Surfactant TA' neither significantly promoted nor inhibited bacterial proliferation of this Gram-negative organism.

3. Precautions and Commentary

None of the surfactant agents described have yet been approved for routine clinical use in neonates in the United States and Europe. 'Surfactant TA' has been approved in Japan for routine clinical use after evidence of respiratory failure in infants with respiratory distress syndrome. To date, the various agents under evaluation in infants have only been compared to conventionally ventilated infants with respiratory distress syndrome. 'CLSE' or 'Surfactant TA', given as a single dose (≈100 mg/kg) to 'prevent' the syndrome, or the post-ventilatory administration (rescue) of infants with established respiratory distress syndrome, have not been shown to reduce mortality in large multicentre trials. In the European trial of single-dose 'Surfactant TA', there was a higher incidence of periventricular-intraventricular haemorrhage (Horbar et al. 1988), although this was not observed in the US studies. The clinical trial of the Collaborative European Multicentre Study Group (1988), using 200mg of 'Curosurf', has demonstrated a striking reduction

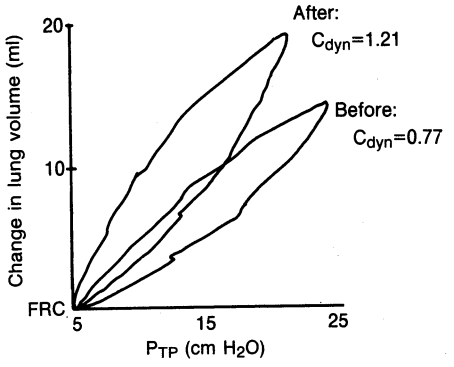

Fig. 5. Changes in lung volume above functional residual capacity (FRC) are plotted against changes in transpulmonary pressure (P_{TP}) in a patient before and after surfactant therapy. There was a significant improvement in tidal volume and dynamic lung compliance (C_{dyn}) after therapy.

of pulmonary air leaks and bronchopulmonary dysplasia, but no effect on the incidence of intraventricular haemorrhage. It is essential that the relative efficacies of the various surfactant preparations be compared directly and that optimal ventilatory techniques are developed when employing surfactant therapy, prior to recommending any specific preparation for human use. Many unanswered questions must be resolved prior to the incorporation of these agents into the neonatologist's pharmacopoeia.

4. Conclusions and Recommendations

A substantial body of clinical data has emerged to document the powerful effects of a variety of surfactants – primarily homologous or modified natural formulations – in modifying the early course of neonatal respiratory distress syndrome. Indeed, the introduction of these agents into neonatal intensive care provides insight into the methodological clinical designs used to establish drug efficacy, rarely witnessed in the uncontrolled introduction of technology into neonatology. Several thousand premature infants have been treated with a variety of agents and while concerns about adverse effects remain, surprisingly few have been encountered. Yet neonatologists cannot be complacent regarding

the complex interactions between these agents and the immune system, host defences and infectious agents, or in the possible overwhelming of mechanisms critical to pulmonary clearance of these exogenously administered drugs that may result in a 'surfactant pneumoconiosis.'

While acute improvements in gas exchange have been characteristic of human or lipid-extracted mammalian surfactants, synthetic surfactant preparations (without SP A, B, or C) appear to be associated with modest acid delay in the improvement of pulmonary function in respiratory distress syndrome. However, survival has been significantly improved in some studies. Most investigators have recognised the advantage of a totally synthesised surfactant which includes the 'critical components' of human surfactant, including disaturated phosphatidylcholine, acidic phospholipids such as phosphatidylglycerol and free fatty acids. Recombinant technologies or peptide synthesis offer the capability to compound surfactants with minimal surface tensions at or near zero, rapid surface adsorption, stability over time and resistance to serum or other inhibitors of surfactant function. These agents should be plentiful, free from foreign protein immunogenicity, and relatively inexpensive to produce. Questions remain regarding ideal combinations of low molecular weight hydrophobic proteins (SP B, C) and phospholipids. SP A may also be a critical component, providing increased stability and metabolic turnover using physiological routes.

Unanswered questions concerning surfactant therapy remain. Optimal dosing, timing, frequency of administration, and resistance to surfactant inhibitors are incompletely answered clinical questions. These questions and others concerning ventilatory techniques to provide uniform deposition within the lung are the focus of clinical trials.

Except in Japan and Finland, surfactant therapy remains investigational. In the United States investigational drug status has permitted the use of selected agents in large numbers of premature infants. While the results of clinical trials are currently under review by regulatory agencies, it is reasonably clear that one or several agents will be approved for use in premature infants with respiratory distress syndrome in the near future. While neonatologists are eager to improve morbidity-free survival for tiny infants, the weight of evidence at present does not necessarily support the contention that improved survival will be associated with reduced morbidity if the absence of bronchopulmonary dysplasia at 28 days is a major criterion for therapeutic success. Thus, prudent practitioners must learn not only how to select appropriate candidates for surfactant therapy, but they must know how to use these agents within the complexities of caring for the many other needs of the very low birthweight infant. These questions and techniques remain a fruitful area of perinatal investigation.

5. Surfactant Treatment of Adult Respiratory Distress Syndrome

Patients with high-permeability lung oedema or the adult respiratory distress syndrome may also be appropriate subjects for surfactant therapy. Early studies of biochemical abnormalities in adult respiratory distress syndrome have shown that it is an acute inflammatory event. An increased number and fraction of polymorphonuclear leucocytes, and high concentrations of their products, are seen in bronchoalveolar lavage fluid from these patients. Those products include collagenase and neutrophil elastase (HNE) [Christner et al. 1985; Lee et al. 1981; McGuire et al. 1980]. In addition, the activated neutrophil produces, through the function of its surface membrane NADPH oxidase, the superoxide radical. Products derived from superoxide are capable of oxidising reactive protein groups, causing lipid peroxidation, and breaking single stranded DNA (Cochrane et al. 1983; Kellog & Fridovich 1977; Schraufstatter et al. 1986). Indeed, several investigators have demonstrated the presence of hydrogen peroxide in the condensed exhaled breath of patients with adult respiratory distress syndrome, either during the illness or just before its appearance (Baldwin et al. 1986; Sznajer et al. 1987).

Both the function and the chemical composition of surfactant recovered from bronchoalveolar

lavage fluid of patients with adult respiratory distress syndrome are abnormal, with a decreased fractional composition of phosphatidylcholine and phosphatidylglycerol, a depression of the lecithin/sphingomyelin ratio, and a marked loss of surface activity (Hallman et al. 1982). Biochemical abnormalities of lung surfactant are present early in respiratory failure, and tend to normalise during recovery.

Surfactant purified by Folch extraction of bronchoalveolar lavage fluid obtained from patients with adult respiratory distress syndrome has increased minimum surface tension (Y_{min}) and time to reach an equilibrium surface tension on the bubble surfactometer (Enhorning 1977). This may be explained by a primary abnormality of surfactant synthesis, involving lipid or protein constituents, an abnormality of assembly of these components, chemical alteration of the components, or the presence of a lipid inhibitor of surfactant function. Although type II pneumocytes are not lost from the acutely injured lung, their production and assembly of surfactant may be impaired, or a material of abnormal composition may be produced.

It is clear that lung surfactant function is impaired in the lungs of patients with adult respiratory distress syndrome. Although minimum surface tension and time to reach equilibrium surface tension are abnormal in surfactant purified by Folch extraction from bronchoalveolar lavage fluid of such patients, those values are markedly more abnormal when equimolar amounts of phospholipid are examined in the original bronchoalveolar lavage fluid. Multiple proteins or glycolipids which may be present in lung epithelial lining fluid (ELF) have been shown to inhibit surfactant function. These include glycolipid (Rauvala & Hallman 1984), albumin (Holm et al. 1985), haemoglobin (Holm & Notter 1987), fibrin monomer (Seeger et al. 1985), bilirubin (Fuchimukai et al. 1987), and a specific surfactant inhibitor (Ikegami et al. 1984). Understanding the interactions between epithelial lining fluid inhibitors of surfactant function and both native and exogenous surfactant will have marked implications for replacement therapy.

In addition to abnormalities of lung surfactant production and the presence of inhibitors of surfactant function, attack by proteases present in epithelial lining fluid on surfactant apoproteins may decrease the function of lung surfactant. In particular, the low molecular weight lung surfactant apoproteins appear to promote rapid adsorption in mixtures of phospholipids, and loss of function of those proteins would diminish lung surfactant function. Human neutrophil elastase is frequently present in epithelial lining fluid and has been shown to be capable of hydrolysing the 35kD apoprotein (Merritt et al. 1987), suggesting one mechanism whereby surfactant from patients with adult respiratory distress syndrome might be altered.

Finally, the evidence that oxygen radicals are present in the lungs of patients with adult respiratory distress syndrome suggests that oxidation of lung surfactant apoproteins or peroxidation of lung surfactant lipids may occur, with deleterious effects on surfactant function. Matalon et al. (1988) found that natural lung surfactant, but not 'CLSE', contained significant amounts of catalase and superoxide dysmatase activity. This antioxidant activity (measured as percentage of hydrogen peroxide or reduction of cytochrome C by O_2 produced) may be a protective mechanism for surfactant.

It would be predicted that loss of surfactant function in adult respiratory distress syndrome by these multiple mechanisms would promote alveolar collapse, leading to loss of lung volume, increased intrapulmonary shunt, and hypoxaemia – major features of the pathophysiology of the syndrome. Furthermore, it has been suggested that diminished surface tension within the alveoli protects against the formation of alveolar oedema, and that loss of surfactant function might therefore promote oedema formation (Bredenberg et al. 1986; Nieman & Bredenberg 1985). Although there may be multiple causes of oedema in the lungs of patients with adult respiratory distress syndrome, loss of surfactant function may be an important contributor.

Considering that surfactant function is diminished in the lungs of patients with adult respiratory distress syndrome and that physiological abnormalities in these patients may be related to this

diminished function, replacement with exogenous surfactant is rational, and may be expected to result in improved lung expansion, with decreased shunt and increased pulmonary compliance. Benefits of these changes would include enhanced blood oxygenation at lower fractions of inspired oxygen, avoidance of toxic levels of oxygen, and use of lower ventilating pressures with reduced barotrauma.

The optimal method of surfactant delivery to maximise its distribution is unknown. Although aerosol delivery has been advocated, that method would require hours to administer the amount of surfactant which is likely to be required. Direct instillation of exogenous surfactant has the advantage of being rapid, and if done correctly may result in homogeneous delivery of the instilled material to the lung periphery.

This method of surfactant replacement has been used by Lachmann to treat several terminally ill patients who had adult respiratory distress syndrome (B. Lachmann, personal communication) and by others to treat 3 adults (Richman et al. 1987). Lachmann found that intratracheal instillation of surfactant suspended in a volume equal to the anatomical dead-space was well tolerated. No improvement in gas exchange was seen until a cumulative dose of >200 mg/kg had been administered.

Richman et al. (1987) reported that the intrabronchial administration of porcine lung surfactant ('Curosurf') in divided doses to each bronchus in 3 patients was well tolerated and caused a modest improvement in gas exchange in all patients. This improvement was transient in 2 patients, and sustained in the third. The surfactant (50 mg/kg) was delivered via a bronchoscope in 5 divided doses – 1 dose to each lobe. The delivery technique required instillation to the more distal lobes first, to avoid obscuring the bronchoscopic field of view. Using a partially blinded crossover experimental design, patients were evaluated for changes in blood oxygenation, lung compliance, and chest radio-graph after having received either surfactant or placebo (air or saline). After receiving surfactant, patients showed a modest (30 to 80 torr) [4.0 to 10.7 kPa] increase in partial pressure of oxygen (paO_2) which was transient (≤ 1 hour) in 2 of the 3 patients. No significant changes in chest radiograph or lung compliance were seen.

Analysis of bronchoalveolar lavage obtained several times after surfactant showed no change in albumin, α_1-proteinase inhibitor specific activity, or cell count. Lavage phospholipid concentrations were elevated at 3 hours and fell by 24 hours (in 2 patients) following therapy. In addition, reduced activity of inhibitor of surfactant function in bronchoalveolar lavage was found after surfactant replacement.

To focus on the possibility that allergic reactions to porcine surfactant might occur, evaluations were undertaken to determine whether immunological sensitivity occurred. It was established that the cutaneous wheal and flare seen in normal adults to >0.1mg surfactant were nonspecific and were not accompanied by blood lymphocyte sensitivity to porcine surfactant. Specifically, blood lymphocytes from persons reacting to intradermal surfactant showed no augmentation of proliferation of interleukin-2 production when stimulated *in vitro*.

In summary, preliminary observations indicate that surfactant replacement therapy for adult respiratory distress syndrome is rational and deserves continuing investigation. Patients who received surfactant appeared to tolerate it well. Determining its efficacy will require additional clinical studies. The surfactant era has now become firmly established in neonatology, yet numerous questions regarding optimal dose requirement for retreatment and ideal measures of efficacy still remain as partially unresolved questions. In the near future one or more of the surfactants used in recent infant clinical trials will be approved by various national regulatory agencies. These agents will become routine therapy, while newer genetically 'engineered' human protein-containing surfactants will be developed; these in turn should be compared to human amniotic fluid surfactant or other heterologous surfactants for their efficacy.

Acknowledgement

Supported by the Sigrid Juselius Foundation, Helsinki, Finland, HL35036, US Public Health Service, FDA 000112 and Sicpa Foundation, Prilly, Switzerland.

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