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Porcine-Derived Lung Surfactant

A Review of the Therapeutic Efficacy and Clinical Tolerability of a Natural Surfactant Preparation (Curosurf®) in Neonatal Respiratory Distress Syndrome

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Synopsis

Porcine-derived lung surfactant (PLS; Curosurf®) has shown efficacy in neonatal respiratory distress syndrome. PLS consists of phospholipids, mainly dipalmitoylphosphatidylcholine, the primary surface-active agent of natural lung surfactant, and pulmonary surfactant-associated proteins which facilitate spreading and adsorption of the surface-active agent at the air-alveolar interface.

Intratracheal administration of a single dose of PLS 200 mg/kg significantly improves the survival rate and reduces the incidence of bronchopulmonary dysplasia at 28 days in premature infants (birthweight 700 to 2000g) with severe respiratory distress syndrome (fraction of inspired oxygen ≥ 0.60). PLS also reduces the incidence of air leak events such as pulmonary interstitial emphysema and pneumothorax. The response rate may be further improved by administration of additional 100 mg/kg doses at 12-hour intervals to infants showing a poor response or relapse after a single dose. PLS prophylaxis reduces the incidence and severity of respiratory distress syndrome in premature infants at high risk of developing the disease; however, it remains unclear whether the eventual clinical outcome is similar or superior to that observed in infants who receive rescue treatment.

PLS is well tolerated and does not appear to increase the incidence of complications of prematurity or respiratory distress syndrome, including patent ductus arteriosus and intraventricular haemorrhage. Although its effect on long term development requires further investigation, early indications are that PLS is not associated with any long term adverse sequelae.

Comparative trials are clearly warranted to determine the efficacy and tolerability of PLS relative to that of other available surfactant preparations, particularly to explore preliminary indications that a more rapid effect of natural surfactants such as PLS (compared with synthetic products) may correlate with improved clinical outcomes, and that PLS may result in fewer complications than synthetic preparations.

Thus, available data show PLS to be a very effective agent for the treatment and prophylaxis of neonatal respiratory distress syndrome, and that it may have some advantages over synthetic preparations.

Neonatal Respiratory Distress Syndrome and Exogenous Surfactant Replacement Therapy

Endogenous lung surfactant lowers surface tension forces at the air-alveolar interface, thereby preventing the alveoli from collapsing during expiration. Its deficiency in premature infants due to lung immaturity at birth can lead to the development of neonatal respiratory distress syndrome. This disease affects about 60 to 70% of infants born at less than 30 weeks' gestation and is associated with high morbidity and increased mortality. The risk of developing respiratory distress syndrome is increased by premature birth, male sex, delivery by caesarean section, being a second-born twin, familial history and maternal diabetes mellitus.

Treatment consists of supplementary oxygen and mechanical ventilation to facilitate gas exchange, and replacement therapy with exogenous lung surfactant. Lung surfactant consists of phospholipids, which are the primary surface-active agents, and pulmonary surfactant-associated proteins, which facilitate adsorption, spreading and recycling of the surfactant within the lungs.

Administration of artificial or natural exogenous surfactant preparations reduces the ventilatory requirement (which can cause complications such as pneumothorax and pulmonary interstitial emphysema) and significantly improves the

clinical outcome in the majority of premature infants with respiratory distress syndrome. However, approximately 10 to 25% of infants show a poor response to surfactant replacement therapy, which may be due to lung immaturity, protein leakage across the alveolar-capillary membrane, disease severity, inadequate dosage, uneven distribution or insufficient levels of surfactant, perinatal asphyxia, patent ductus arteriosus or the presence of congenital infection. Whether there is an increased risk of infection and/or immunological sensitisation to foreign proteins and phospholipids found in exogenous surfactant preparations in infants remains unclear.

Pharmacological Properties of Porcine-Derived Lung Surfactant

Porcine-derived lung surfactant (PLS; Curosurf®) consists of approximately 99% polar lipids (mainly phospholipids) and 1% hydrophobic, low molecular weight proteins (surfactant-associated proteins B and C). The drug significantly improved lung expansion and gas exchange in preterm rabbit pups to a level similar to that seen in near-term ventilated pups and appeared more effective than various artificial surfactant preparations in this regard. PLS has also shown efficacy in adult guinea-pigs with severe respiratory insufficiency induced by lung lavage and in a rabbit model of meconium aspiration.

Inhibition of the surface properties of PLS by plasma proteins (fibrinogen > haemoglobin > albumin) has been demonstrated *in vitro* at protein : surfactant concentration ratios of >1 : 1.

Clinical Efficacy

PLS administered as rescue therapy significantly improved clinical outcome in premature infants with severe respiratory distress syndrome [birthweight 700 to 2000g; fraction of inspired oxygen (FiO_2) ≥ 0.60] in randomised multicentre trials. Compared with untreated controls, intratracheal administration of a single bolus of PLS 200 mg/kg 2 to 15 hours after birth caused significant improvements in gas exchange and oxygenation, which were evident within 5 minutes of drug administration.

The 28-day mortality rate was significantly lower in PLS recipients versus untreated controls (31 *vs* 51%), the incidence of bronchopulmonary dysplasia in survivors was reduced by about 57% (23 *vs* 53%), and there was an increase in the combined incidence of survival without bronchopulmonary dysplasia compared with untreated controls (55 *vs* 26%). Administration of additional 100 mg/kg doses at 12-hour intervals to infants still requiring high supplemental oxygen after the first dose further reduced the 28-day mortality rate with or without bronchopulmonary dysplasia. Furthermore, the mortality rate was lower in infants treated at an earlier stage of the disease (FiO_2 0.40 to 0.59) compared with late treatment once the disease became severe ($FiO_2 \geq 0.60$).

PLS prophylaxis in premature infants (26 to 29 weeks' gestation) significantly reduced the incidence and severity of respiratory distress syndrome compared with controls (incidence of severe respiratory distress syndrome 19 *vs* 36%), and reduced the 28-day mortality rate from 19 to 11%. However, the clinical outcome at 28 days did not differ significantly between infants receiving prophylaxis and those eligible for rescue treatment. Findings of a recent meta-analysis suggest that prophylaxis is more beneficial than rescue treatment; thus larger trials comparing the efficacy of these 2 treatment regimens are warranted, as are studies to identify subgroups of infants likely to receive the most benefit from PLS prophylaxis. While preliminary findings suggest that natural surfactants such as PLS may act

more rapidly than synthetic surfactants, comparative clinical studies with other surfactant preparations are lacking.

Clinical Tolerability

PLS administration has been well tolerated in multicentre clinical trials (including >2900 patients), in which it did not appear to increase the incidence of complications of prematurity or respiratory distress syndrome in premature infants (700 to 2000g birthweight). Premature infants treated with PLS had a lower incidence of pulmonary air leak events (pulmonary interstitial emphysema and pneumothorax), and the number of infants with patent ductus arteriosus, intraventricular haemorrhage, retinopathy of prematurity, pneumonia, septicaemia or necrotising enterocolitis did not appear to differ significantly between PLS recipients and untreated or historical controls. PLS does not appear to increase the incidence of apnoea of prematurity or pulmonary haemorrhage; however, this requires further study.

Preliminary results at 2-year follow-up indicate that PLS administration at birth does not appear to affect the incidence of functional handicaps or overall growth and development compared with no treatment, and does not appear to adversely affect immunological sensitisation to lung surfactant compared with that observed in untreated controls. However, the longer term tolerability of surfactant replacement therapy as measured by effects on development remains unclear.

Dosage and Administration

PLS 100 or 200 mg/kg administered intratracheally as a single bolus (concentration 80 g/L; total volume 1.25 or 2.5ml) over a few seconds is recommended to treat premature infants with established respiratory distress syndrome (birthweight 700 to 2000g). Infants still requiring supplemental oxygen 12 hours postdose ($FiO_2 > 0.40$) may be given an additional 100 mg/kg dose, and a further dose (100 mg/kg) may be given 12 hours later if FiO_2 remains above 0.40. Infants at high risk of developing respiratory distress syndrome may be treated with a single 100 or 200 mg/kg dose within 10 minutes of birth as prophylaxis.

Porcine-derived lung surfactant (PLS; Curosurf®) has shown efficacy in the treatment and prevention of respiratory distress syndrome in premature infants. This condition affects about 60 to 70% of infants born at less than 30 weeks' gestation and is the cause of high morbidity and increased mortality. The following article provides a brief overview of neonatal respiratory distress syndrome and exogenous surfactant replacement therapy, which has been reviewed extensively elsewhere,[1-6] and focuses on the clinical efficacy and tolerability of PLS in this indication.

1. Overview of Neonatal Respiratory Distress Syndrome and Exogenous Surfactant Replacement Therapy

1.1 Respiratory Distress Syndrome

Neonatal respiratory distress syndrome (also known as hyaline membrane disease) is caused primarily by a deficiency of endogenous lung surfactant due to pulmonary immaturity at birth.[7] Lung surfactant is necessary to lower surface tension forces at the air-alveolar interface, thereby preventing the alveoli from collapsing during expiration. Thus, its role is instrumental in maintaining gas exchange and decreasing the work associated with breathing. Furthermore, surfactant serves as a lubricant, protecting the airways and promoting mucociliary transport. Premature infants lacking adequate surfactant at birth need to achieve increasingly higher inspiratory pressures to re-expand the alveoli and accomplish adequate gas exchange. As the infant tires, hypoxia and acidosis occur and progressive pulmonary failure develops.

The risk of developing respiratory distress syndrome increases as gestational age decreases. Other risk factors include male gender, delivery by

caesarean section without labour, being a second-born twin, familial history and maternal diabetes mellitus.[6] Interestingly, factors that place the fetus under stress *in utero*, such as prolonged rupture of the membranes, maternal narcotic addiction, and intrauterine growth retardation, may lower the risk of respiratory distress syndrome.[6] Antenatal administration of hormones (glucocorticoids) that accelerate fetal lung maturation and prophylactic administration of exogenous lung surfactant soon after birth lower the disease incidence, and appear to have synergistic beneficial effects on neonatal lung function.[8]

Diagnosis of respiratory distress syndrome is based upon clinical symptoms and radiological findings characterising the severity of the disease.[9] Chest radiological findings show a reticulogranular pattern, and clinical signs including tachypnoea, expiratory grunting, cyanosis and intercostal retractions are evident within hours of birth. Measurements of ventilation and lung mechanics are also valuable, as are biochemical studies, which provide direct evidence of pulmonary surfactant deficiency.[9] The disease is considered severe in infants with a fraction of inspired oxygen (FiO_2) > 0.60 or an arterial/alveolar PO_2 ratio (a/A PO_2) < 0.14 and moderate in infants with an FiO_2 0.41 to 0.59 and a/A PO_2 ratio < 0.20 to 0.14.

1.2 Exogenous Surfactant Replacement Therapy

Treatment of respiratory distress syndrome consists of supplemental oxygen with mechanical ventilation to facilitate gas exchange, and surfactant replacement therapy with exogenous natural or artificial surfactant. Although mechanical ventilation is invaluable in reducing mortality by facilitating gas exchange and preventing alveolar collapse, there are associated complications such as bronchopulmonary dysplasia or chronic lung disease (a condition characterised by chronic morphological and functional damage to the lungs) and pulmonary air leak events (pneumothorax and pulmonary interstitial emphysema).

These complications may be reduced by exogenous lung surfactant therapy, which improves lung function and thereby reduces the requirement for mechanical ventilation.

Natural human lung surfactant, which is synthesised and stored in alveolar type II pneumocytes, is composed of phospholipids (85%), neutral lipids (10%) and pulmonary surfactant-associated proteins (apolipoproteins; 5%) [table I]. The phospholipids are the primary surface-active ingredients that lower the surface tension forces contributing to alveolar collapse.[1] Dipalmitoylphosphatidylcholine (fig. 1) is the most abundant and active phospholipid found in natural surfactant and is the major constituent of exogenous surfactant preparations. Proteins facilitate adsorption, spreading and recycling of the surfactant within the lungs as well as having immunomodulatory properties.[1] Surfactant protein A (SP-A) and SP-D have both shown immunomodulatory properties; SP-A having been found to increase the microbial killing function of alveolar macrophages and in-

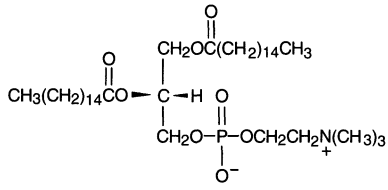

Fig. 1. Chemical structure of dipalmitoylphosphatidylcholine, the primary surface-active agent in natural and synthetic surfactant preparations.

Table I. Composition of endogenous lung surfactant (approximate % of surfactant composition)

Phospholipids (85%)
Dipalmitoylphosphatidylcholine (45 to 70%)
Phosphatidylcholine
Phosphatidylglycerol
Phosphatidylinositol
Phosphatidylethanolamine
Phosphatidylserine
Sphingomyelin
Others
Neutral lipids (10%)
Apolipoproteins (5%)
Surfactant proteins A, B, C and D

crease the resistance of the lipoid surface complex against inhibitors of surface activity.[10,11]

Table II provides a summary of the different exogenous preparations investigated to date. PLS is one of the natural surfactants derived from an animal source.

Fujiwara et al.[13] first demonstrated the clinical efficacy of exogenous surfactant in producing marked improvements in oxygenation and gas exchange in premature infants with respiratory distress syndrome. Subsequent studies have confirmed these findings and shown a significant reduction in morbidity and mortality following artificial or natural surfactant administration (for recent reviews see Gortner;[2] Hallman et al.;[12] Jobe et al.;[3] Speer & Halliday[5]). The incidence of barotraumatic pulmonary complications (pneumothorax and pulmonary interstitial emphysema) has been reduced by up to 80% and neonatal mortality by about 30 to 40%, while survival rates without lung disease have increased by about 17%.[5,12]

Approximately 10 to 25% of infants show a poor response to surfactant replacement therapy;[2]

Table II. Exogenous surfactant preparations which have been investigated for the treatment of neonatal respiratory distress syndrome[12]

Surfactant source	Composition
Artificial surfactants	
Synthetic	DPPC, unsaturated phosphatidylglycerol
Synthetic	DPPC, hexadecanol, tyloxapol
Human surfactants	
Amniotic fluid	Surfactant lipids, SP-A, SP-B, SP-C
Animal surfactants	
Lipid extract of bovine lung lavage	Surfactant lipids, SP-B, SP-C
Lipid extract of bovine lung	Surfactant lipids, SP-B, SP-C
Lipid extract of porcine lung purified by chromatography	Surfactant phospholipids, SP-B, SP-C
Lipid extract of bovine lung surfactant + added synthetic lipids	Surfactant lipids + DPPC, tripalmitin, palmitic acid

Abbreviations: DPPC = dipalmitoylphosphatidylcholine; SP-A = surfactant protein A; SP-B = surfactant protein B; SP-C = surfactant protein C.

Table III. Factors with a negative influence on the clinical efficacy of surfactant replacement therapy[2,14,15]

- Congenital bacterial infection (sepsis or pneumonia)
- Very immature lungs
- Pulmonary oedema secondary to immaturity
- Inactivation of surfactant by leakage of proteins across the alveolar-capillary membrane
- Patent ductus arteriosus
- Perinatal asphyxial injury
- Male gender
- Severe disease prior to treatment

associated factors are summarised in table III. The extent of protein leakage (including fibrinogen and albumin) across the alveolar-capillary membrane, causing inactivation of the surface properties of surfactant, is dependent on the degree of lung immaturity and extent of lung lesions secondary to mechanical ventilation and impaired oxygenation and circulation.[2,15] Thus, *in vitro* studies showing differential sensitivity of exogenous surfactant preparations to inhibitory proteins may have important implications in the clinical setting.[16,17] Poor response may also be due to pulmonary disorders which can mimic respiratory distress syndrome but which are not caused by surfactant deficiency. For example, infants with congenital infection may present with symptoms indistinguishable from respiratory distress syndrome, but have a poor response to surfactant replacement. Poor response may also be due to insufficient dosage of surfactant, uneven distribution of exogenous surfactant and/or insufficient levels of surfactant in the epithelial lining fluid.[12]

Concern has been raised about the possible risk of infection and/or immunological sensitisation to foreign proteins and phospholipids found in surfactants derived from animal sources. Although studies have shown the presence of antibodies recognising animal surfactant proteins in premature infants,[18-21] the short and long term effects of this immune reactivity remain to be determined. In fact, the ability of exogenous surfactant replacement therapy to reduce lung damage and consequently limit surfactant protein leakage into the circulation may actually reduce immune sensitisa-

tion to surfactant.[22] Furthermore, natural surfactant therapy has been found to suppress monocyte tumour necrosis factor secretion, thereby down-regulating inflammatory reactions in the lung.[23]

The clinical significance of platelet-activating factor (PAF) present in natural surfactant preparations remains unclear.[24] PAF has been found in natural surfactant preparations from animal sources at concentrations capable of eliciting a physiological effect in the lungs of neonates.[24] Possible detrimental effects of PAF on lung tissue include increased vascular resistance, bronchoconstriction and oedema secondary to activation of leukotriene production, whereas possible beneficial effects include enhanced glycogen breakdown and synthesis, and secretion of surfactant.[24]

2. Pharmacological Properties of Porcine-Derived Lung Surfactant

PLS is a natural surfactant which has been extracted from minced porcine lungs by a combination of washing, chloroform-methanol extraction and liquid-gel chromatography. It contains approximately 99% polar lipids (mainly phospholipids) and 1% hydrophobic, low molecular weight proteins (SP-B and SP-C).[25-28] PLS is devoid of cholesterol, triglycerides, cholesteryl esters and SP-A,[28,29] but contains PAF (about 0.1 μmol/L).[24]

The efficacy of PLS as surfactant replacement therapy was initially demonstrated in preterm newborn rabbits, which serve as a useful model for neonatal respiratory distress syndrome. Rabbit neonates born after 27 days' gestation (term = 31 days) succumb quickly to respiratory distress syndrome attributable to a combination of surfactant deficiency and poor ventilatory efforts. If kept alive by artificial ventilation, they develop bronchiolar and alveolar lesions similar to those seen in infants with respiratory distress syndrome, and there is a considerable leakage of protein into the alveolar spaces.[30]

After instillation of PLS into the airways of artificially ventilated preterm newborn rabbits, significant improvements were observed in lung expansion and gas exchange within 30 minutes of

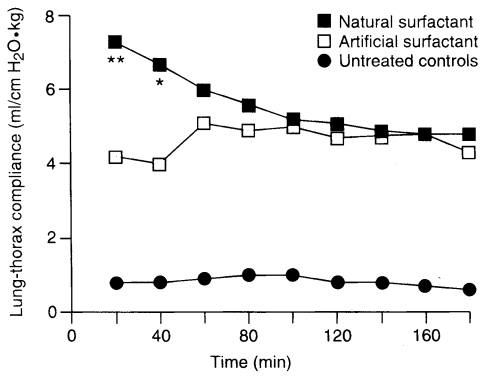

Fig. 2. Lung-thorax compliance in untreated premature newborn rabbit pups (n = 20) or pups treated with natural [porcine- (n = 22) or bovine-derived (n = 10)] or artificial (n = 10) surfactant during a 3-hour period of artificial ventilation.[30] Mean values estimated from graphically presented data. * $p < 0.01$; ** $p < 0.001$ *vs* artificial surfactant.

administration compared with untreated controls.[30-33] Lung-thorax compliance was improved to a level similar to that observed in near-term animals ventilated under similar conditions, and the mortality rate was significantly reduced.[30,33]

While comparative studies in humans are lacking, PLS has shown superior efficacy to artificial (synthetic) surfactant preparations in improving lung-thorax compliance (fig. 2) and alveolar expansion in premature rabbit pups.[30,34,35] Following treatment with saline (control), PLS 2.5 ml/kg or a synthetic surfactant 5 ml/kg (consisting of dipalmitoylphosphatidylcholine, hexadecanol and tyloxapol), tidal volumes recorded at an insufflation pressure of 25cm H_2O were significantly improved in surfactant treatment groups compared with the controls.[34] Tidal volume was also significantly increased in PLS-treated animals at insufflation pressures of 20 and 15cm H_2O, whereas artificial surfactant had no significant effect. The mean end expiratory lung gas volume was increased by 20-fold in PLS-treated animals ($p < 0.001$ *vs* controls), while an increase of only 4- to 8-fold was observed in animals treated with synthetic surfactant ($p < 0.001$ *vs* PLS). In addition,

the expiratory time constant after 5 and 30 minutes of ventilation was prolonged by about 100% in PLS-treated animals. In animals treated with artificial surfactant, expiratory time constant did not differ significantly from controls after 5 minutes, but was prolonged after 30 minutes versus controls, although it remained significantly shorter than in PLS-treated animals. These differences reflect a failure in lung stabilisation in animals treated with artificial surfactant which may be due to the absence of specific hydrophobic proteins which are present in PLS and other natural surfactants.

Surfactant replacement therapy with PLS was also effective in adult guinea-pigs with severe respiratory insufficiency induced by repeated lung lavage. PLS reduced the development of epithelial lesions and prevented the leakage of proteinaceous oedema fluid into the air spaces, indicating that it may be an effective therapy for adult forms of respiratory insufficiency caused by deficiency or inactivation of pulmonary surfactant.[36,37]

In a rabbit model of meconium aspiration, a condition which occurs mainly in term and post-term infants usually as a consequence of intrauterine asphyxia, PLS improved lung-thorax compliance and reduced the minimum surface tension of bronchoalveolar lavage fluid.[38] Furthermore, lung changes induced by meconium aspiration (including atelectasis and oedema) were ameliorated by exogenous surfactant in a dose-dependent way. The therapeutic efficacy of PLS in infants with this syndrome remains to be determined.

PLS and a bovine lung surfactant extract showed similar sensitivity to inhibition by plasma proteins; both being dose-dependently inhibited by fibrinogen > haemoglobin > albumin at protein : surfactant ratios >1 : 1.[17] However, these surfactants were inhibited to a greater extent than 2 other surfactants extracted from calf lung or bovine lavage fluid, which were only moderately inhibited by fibrinogen and not inhibited by haemoglobin or albumin up to protein : surfactant concentration ratios of 2 : 1 (see section 1.2).

3. Clinical Efficacy of Porcine-Derived Lung Surfactant in Neonatal Respiratory Distress Syndrome

3.1 Rescue Treatment

PLS has proven effective for the treatment of infants with established respiratory distress syndrome requiring ventilatory support and supplemental oxygen (rescue treatment) in large multicentre randomised studies;[26,29,39-41] (table IV) and in small studies involving about 10 to 20 patients.[27,42-46] The efficacy of a single 200 mg/kg dose has been compared with no treatment, and multiple dose studies have investigated the optimal dosage and timing of PLS administration. However, there is a lack of comparative clinical trials which hinders direct assessment of the efficacy of PLS in relation to that of other surfactant preparations.

The investigators and caregivers were generally not blinded in these clinical trials. Criteria for inclusion in clinical trials have included clinical and radiological findings typical of respiratory distress syndrome (see section 1.1), birthweight 700 to 2000g, $FiO_2 \geq 0.60$ (severe disease), requirement for artificial ventilation, and no evidence of complicating disease. Infants meeting these criteria 2 to 15 hours after birth and randomised to treatment with PLS were disconnected from the respirator while the drug was administered intratracheally.

Clinical efficacy was evaluated by determining: the severity of respiratory distress syndrome after treatment (measured by gas exchange, and inspired oxygen and ventilatory requirements), the incidence of bronchopulmonary dysplasia (prolonged oxygen dependency and/or abnormal chest radiological findings;[47] and the mortality rate from respiratory distress syndrome at 28 days.

3.1.1 Single Dose Studies

The Collaborative European Multicenter Study Group[26] compared the efficacy of a single dose of PLS 200 mg/kg with that of no treatment in 146 infants with severe respiratory distress syndrome (mean FiO_2 0.8) in 8 European neonatal intensive care units. Infants randomised to the untreated con-

Table IV. Results of randomised multicentre studies of the clinical efficacy of porcine-derived lung surfactant (PLS) in premature infants (birthweight 700 to 2000g) with respiratory distress syndrome (RDS)

Reference	Treatment (mg/kg)	No. of evaluable infants	Ventilatory requirement (days)	Inspired oxygen requirement (days)	Incidence of BPD in survivors (%)	Mortality (%)		Mortality and/or BPD (%)
						≤10 days	≤28 days	
Single dose studies								
Bevilacqua et al.[29]	PLS 200 (early)[a]	86	5.2‡‡	10‡	9		9‡	18‡
	PLS 200 (late)[a,b]	96	7	12.5	14		23	34
Collaborative European Multicenter Study Group[26]	C	69	10.5		53	48	51	74
	PLS 200	77	7		23*	22**	31*	45***
Multiple dose studies								
Halliday et al.[40]	PLS 100 × 3[c]	1069	6				21	51
	PLS 200 + 100 × 4[d]	1099	5				20	51
Speer et al.[41]	PLS 200	176	13	18.5	15	17	21	33
	PLS 200 + 100 × 2[e]	167	15	17.5	15	13	13†	27

a Early administration of PLS to infants at moderately severe stage of RDS (FiO_2 0.40 to 0.59) or late administration to infants with severe disease ($FiO_2 \geq 0.60$).

b 51% of infants (n = 49) developed severe disease and were eligible for rescue treatment.

c An initial dose of PLS 100 mg/kg was administered 2 to 15 hours after birth and 2 further doses of 100 mg/kg were administered at 12-hour intervals after the first dose if required.

d An initial dose of PLS 200 mg/kg was administered 2 to 15 hours after birth and 4 further doses of 100 mg/kg were administered at 12-hour intervals after the first dose if required.

e An initial dose of PLS 200 mg/kg was administered 2 to 15 hours after birth and 2 further doses of 100 mg/kg were administered at 12-hour intervals after the first dose if required.

Abbreviations and symbols: BPD = bronchopulmonary dysplasia; C = untreated controls; ‡ $p < 0.05$ *vs* late treatment; ‡‡ $p < 0.01$ *vs* late treatment; * $p < 0.05$ *vs* controls; ** $p < 0.01$ *vs* controls; *** $p < 0.001$ *vs* controls; † $p < 0.05$ *vs* single dose;.

trol group were disconnected from the respirator and ventilated manually for a few minutes (similar to treated infants), but no sham intratracheal administration procedure was performed. Treated and control groups were well matched for gestational age, birthweight, gender, age at entry and oxygen requirement before treatment. Compared with controls, infants treated with PLS showed a rapid and significant improvement in the severity of respiratory distress syndrome. Improvements in gas exchange and oxygenation were evident within 5 minutes of intratracheal PLS administration; the FiO_2 being reduced to about 0.4 (moderate disease) within 3 to 4 days in treated subjects, while at least 6 days were required to reach this value in untreated controls. In addition, a significant reduction was observed in mean airway pressure after 4 hours (fig. 3). Reductions in peak insufflation pressure, inspiration : expiration ratio and respiratory frequency were also found. Although the overall requirement for artificial ventilation was lower in PLS-treated infants versus controls (7 *vs* 10.5 days), the difference did not reach statistical significance.

PLS administration significantly improved clinical outcome compared with controls (table IV). The 28-day mortality rate was 31 *vs* 51% ($p < 0.05$) and the incidence of bronchopulmonary dysplasia amongst treated and untreated survivors at 28 days was 23 versus 53%. In addition, the combined incidence of survival without bronchopulmonary dysplasia was 55 versus 26% in the 2 groups, respectively ($p < 0.001$).

The high mortality rate in this study may reflect the severity of the disease in the infants treated (mean FiO_2 about 0.8). In a subsequent study per-

formed the following year at the same neonatal intensive care units in which another 87 infants were treated with a single dose of PLS 200 mg/kg, the mortality rate was 15% while the survival rate without evidence of bronchopulmonary dysplasia was similar to that reported in the previous study.[14] Because of the proven efficacy of PLS in the earlier study, no control group was used in this later study for ethical reasons.

The results of these 2 studies are supported by findings from smaller studies, which reported rapid improvements in oxygenation and gas exchange within 15 minutes of administration of a single 200 mg/kg dose of PLS, a significantly lower oxygen requirement compared with that observed in untreated controls, and reduced mortality at 28 days.[42-46]

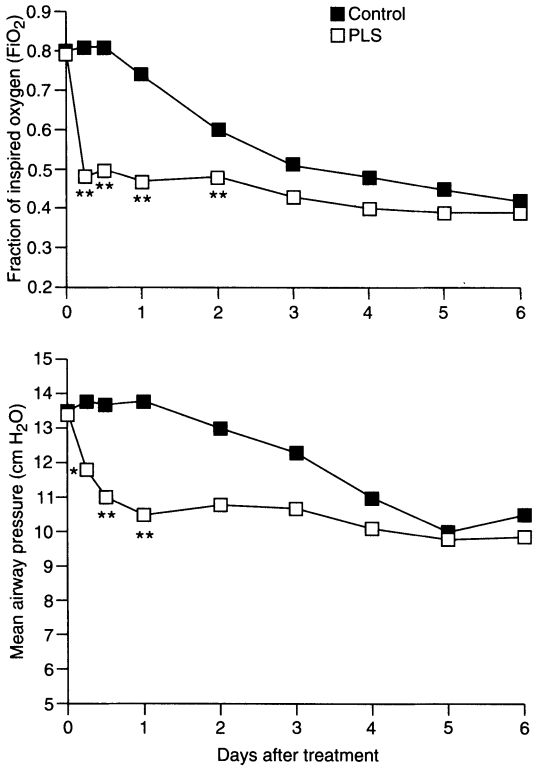

Fig. 3. Fraction of inspired oxygen and mean airway pressure following treatment with a single dose of porcine-derived lung surfactant (PLS) 200 mg/kg (n = 77) or no treatment (control: n = 69) 2 to 15 hours after birth in premature infants (700 to 2000g birthweight) with respiratory distress syndrome.[26] * $p < 0.01$; ** $p < 0.001$ vs control.

The efficacy of a single dose of PLS 200 mg/kg administered at different stages in the development of respiratory distress syndrome was investigated in a randomised multicentre study[29] (table IV). Infants with moderately severe disease (FiO_2 0.40 to 0.59) were randomised to receive early treatment with PLS 200 mg/kg (n = 86) while those in the late treatment group only received PLS if or when the disease became severe ($FiO_2 \geq 0.60$; n = 96). In the latter group, 49 infants (51%) developed severe disease and were eligible for late surfactant replacement therapy. Immediate treatment with PLS when the disease was moderately severe significantly improved the clinical outcome versus no or late treatment at the severe stage (table IV). Infants who received immediate treatment had a significantly lower requirement for mechanical ventilation ($p < 0.01$) and supplementary oxygen ($p < 0.05$) compared with those in the late treatment group. The 28-day mortality rate was 9 *vs* 23% ($p < 0.05$), and the combined incidence of mortality and/or bronchopulmonary dysplasia was 18 *vs* 34% ($p < 0.05$). Although the incidence of bronchopulmonary dysplasia in survivors was lower in the early treatment group (9 *vs* 14%), the difference did not reach statistical significance. Thus, it appears that treatment with PLS when respiratory distress syndrome is moderately severe can prevent or reverse its natural progression in some infants.[29]

3.1.2 Multiple Dose Studies

The administration of 2 additional doses of PLS 100 mg/kg at 12-hour intervals to infants still requiring supplementary oxygen ($FiO_2 > 0.21$) after an initial 200 mg/kg dose further reduced the severity of respiratory distress syndrome in the first 2 days of life (fig. 4) and significantly improved the survival rate at 28 days compared with a single 200 mg/kg dose[41] (table IV). The overall duration of inspired oxygen and ventilatory requirements were similar in infants randomised to the single-dose (n = 176) or multiple-dose (n = 167) treatment groups (18.5 *vs* 17.5 days, and 13 *vs* 15

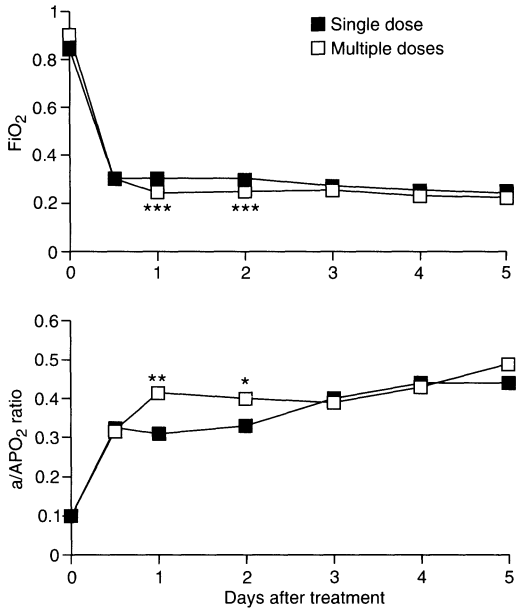

Fig. 4. Measurements of gas exchange and oxygenation in premature infants after treatment with a single dose of porcine-derived lung surfactant 200 mg/kg (n = 176) or an initial dose of 200 mg/kg followed by 2 additional 100 mg/kg doses 12 hours apart if required (n = 167).[41] *Abbreviations and symbols:* a/APO_2 = arterial/alveolar PO_2 ratio; FiO_2 = fraction of inspired oxygen; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ *vs* single dose.

days, respectively); however, mortality rates at 28 days were significantly lower in infants receiving multiple doses (13 *vs* 21%; $p < 0.05$). Although the combined outcome of mortality and bronchopulmonary dysplasia at 28 days was lower in the multiple dose treatment group (27 *vs* 33%), the difference did not reach statistical significance, and the incidence of bronchopulmonary dysplasia amongst survivors was the same in both treatment groups (15%).

Halliday et al.[40] compared the efficacy of a low (100 mg/kg) and high (200 mg/kg) initial dose of PLS followed by additional 100 mg/kg doses at 12-hour intervals [for up to 24 hours in the low dose group (n = 1069; 300mg total) and for up to 72 hours in the high dose group (n = 1099; 600mg total)] in infants with moderate to severe respiratory distress syndrome ($a/A\ PO_2 < 0.22$). Although the higher dosage regimen improved oxygenation and gas exchange compared with the lower dosage in the first 3 days (percentage of infants still requiring >40% oxygen after 3 days was 48 and 43% in the low and high dose groups, respectively; $p < 0.01$), these early benefits were not reflected in improved clinical outcome, which was the same in both treatment groups (mortality 21 *vs* 20%, mortality and/or bronchopulmonary dysplasia 51% at 28 days; table IV).

3.1.3 Comparative Studies

At present, there is a lack of studies comparing the clinical efficacy of PLS with that of other currently available surfactant preparations. A single randomised nonblinded multicentre study has compared the efficacy of PLS with that of a natural bovine-derived lung surfactant preparation in premature infants with respiratory distress syndrome requiring artificial ventilation with $FiO_2 \geq 0.40$.[48] 75 infants were randomised 24 hours after birth to treatment with either PLS 200 mg/kg (followed by up to 2 additional 100 mg/kg doses if required ie. $FiO_2 \geq 0.30$) or a bovine-derived surfactant preparation 100 mg/kg (followed by up to 3 additional 100 mg/kg doses). Both treatment groups showed a significant and rapid improvement in oxygenation after surfactant administration, and a reduction in the ventilatory requirement. These parameters were improved to a greater extent in PLS-treated infants up to 24 hours after initiation of therapy.

There was no significant difference in the clinical outcome at 28 days between treatment groups, although the mortality rate was lower in PLS recipients (3 *vs* 12.5%). Larger comparative studies are clearly warranted to identify differences of clinical significance between surfactant preparations.

3.2 Prophylactic Use

The efficacy of PLS prophylaxis, compared with rescue treatment, in reducing the incidence of respiratory distress syndrome and in improving clinical outcome has been examined in a randomised nonblinded study.[49] Premature infants (gestational age 26 to 29 weeks) randomised to PLS prophylaxis (n = 75) received a single 200

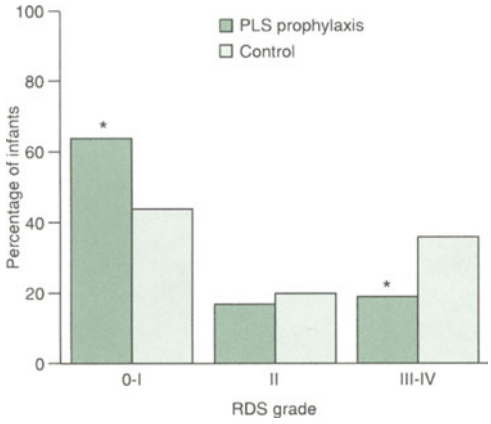

Fig. 5. Incidence and severity of respiratory distress syndrome (RDS) [Grade 0-I, none or mild; II, moderate; III-IV, severe] 6 hours after birth in premature infants randomised to receive prophylaxis with porcine-derived lung surfactant (PLS) 200 mg/kg 10 minutes after birth (n = 75) or no treatment followed by rescue treatment with porcine-derived lung surfactant 200 mg/kg after 6 hours if necessary (control; n = 72).[49] *$p < 0.05$ *vs* control.

mg/kg dose within 10 minutes of birth, while infants randomised to no treatment or rescue therapy (n = 72) received no surfactant at birth but were intubated and subjected to the same ventilatory manoeuvres as the prophylaxis group and were treated with PLS after 6 hours if necessary ($FiO_2 \geq 0.60$).

Respiratory distress syndrome was significantly less severe 6 hours after birth in the group of infants treated with PLS prophylaxis compared with the control group (fig. 5). Severe respiratory distress syndrome occurred in 19% of PLS-treated infants compared with 36% of controls ($p < 0.05$), and the proportion of infants with no or mild disease was 64 and 44% in the 2 treatment groups, respectively ($p < 0.05$). Consequently, the percentage of infants requiring rescue treatment 6 to 24 hours after birth was significantly lower in the group receiving prophylactic therapy (11 *vs* 32%; $p < 0.01$).

The 28-day mortality rate was lower in infants receiving PLS prophylaxis than in those receiving rescue treatment (11 *vs* 19%), although the difference was not statistically significant. Furthermore, the incidence of bronchopulmonary dysplasia was similar in both treatment groups (29 *vs* 24%), indicating that the initial benefits observed following PLS prophylaxis (reduced incidence and severity of respiratory distress syndrome) were not reflected in an overall improvement in clinical outcome compared with rescue treatment. The findings of a recent meta-analysis of 3 clinical studies indicate, however, that PLS prophylaxis does significantly improve clinical outcome versus rescue treatment.[50] After stratifying the results for gestational age and the typical odds ratios (± 95% confidence limits), the incidences of severe respiratory distress syndrome and of mortality were significantly lower in the prophylaxis groups, as was the incidence of bronchopulmonary dysplasia among survivors. Larger comparative trials are clearly warranted to identify any significant differences between PLS prophylaxis and rescue treatment, and to identify subgroups of infants which are most likely to benefit from prophylaxis.

4. Clinical Tolerability

PLS has been well tolerated in large multicentre clinical trials to date (including a total of more than 2900 infants), in which it did not appear to significantly increase the incidence of complications associated with prematurity and respiratory distress syndrome compared with that reported in untreated or historical controls (summarised in table V).

4.1 Pulmonary Air Leak Events

Excessive mechanical ventilation in infants with respiratory distress syndrome can lead to diffuse alveolar rupture and result in pulmonary interstitial emphysema, which can in turn progress to pneumothorax and other types of air leak phenomena. Compared with no treatment, PLS administration significantly reduced the incidence of both pulmonary interstitial emphysema and pneumothorax.[26] The incidence of pneumothorax in controls and PLS recipients was 35 *vs* 18% ($p < 0.05$) and that of pulmonary interstitial emphysema was 39 *vs* 23% ($p < 0.05$). Administration of additional doses of PLS 100 mg/kg to infants not showing a

Table V. Incidence of complications associated with prematurity or respiratory distress syndrome in premature infants (700-2000g birthweight) treated with porcine-derived lung surfactant (PLS) [rescue (PLSR) or prophylaxis (PLSP)] or in untreated controls (C) in large multicentre clinical trials; data are presented as the percentage of total infants treated

Treatment (mg/kg)[a]	No. of infants	Pulmonary interstitial emphysema	Pneumo-thorax	Patent ductus arteriosus	Intracerebral haemorrhage (grades III-IV)[b]	Pulmonary haemorrhage	Retinopathy of prematurity	Pneumonia	Septicaemia	Necrotising enterocolitis
PLS *vs* control[26]										
PLSR 200	69	23*	18*	60	26			14		
C	77	39	35	46	23			20		
PLS single *vs* multiple doses[41]										
PLSR 200	176	27	18	52	20	2			20	3
PLSR 200 (+ 2 x 100)	167	23	9**	57	23	2			13	3
PLS low *vs* high doses[40]										
PLSR 100 (+ 2 x 100)	1069		19	36		6	5	11		5
PLSR 200 (+ 4 x 100)	1099		16	36		7	4	12		7
PLS prophylaxis *vs* rescue[49]										
PLSP 200	75	3	3	31	11					
PLSR 200	72	1	7	22	10					
PLS early *vs* late treatment[29]										
PLSR 200 (early)	86	6	6	33	7†		7	20	7	1
PLSR 200 (late)	96	15	14	25	18		3	15	12	5

a In infants randomised to the multiple dose treatment groups, additional doses were administered at 12-hour intervals to infants if the fraction of inspired oxygen was still > 0.21.

b Papile et al.[51] classification.

Symbols: * $p < 0.05$ *vs* untreated controls; ** $p < 0.01$ *vs* single-dose; † $p < 0.05$ *vs* late treatment.

satisfactory response to a single dose (200 mg/kg) further reduced the incidence of pulmonary air leak events compared with a single dose, the reduction in incidence of pneumothorax reaching statistical significance (18 *vs* 9%; $p < 0.01$).[41] Immediate treatment of infants with moderately severe disease was associated with a lower, but not statistically significant, incidence of pneumothorax (6 *vs* 14%) and pulmonary interstitial emphysema (6 *vs* 15%) than treatment at the more advanced stage of the disease,[29] whereas the incidence of pulmonary air leak events was similar in infants treated with PLS prophylaxis or rescue therapy.[49]

4.2 Patent Ductus Arteriosus

The incidence of patent ductus arteriosus generally ranges from 15 to 36% in premature infants, but this is dependent on the degree of prematurity and occurrence of pulmonary disease; the incidence being significantly higher (about 75 to 80%) in infants with respiratory distress syndrome born at less than 30 weeks' gestation.[52]

Although PLS administration increased the incidence of patent ductus arteriosus compared with no treatment, the difference did not reach statistical significance (60 *vs* 46%), and the incidence of PDA amongst survivors in the PLS and control groups was similar (58 *vs* 53%).[26] The incidence was similar in infants treated with single or multiple doses of PLS,[41] but tended to be higher in infants receiving prophylaxis than in those receiving rescue therapy (31 *vs* 22%).[49]

4.3 Intracerebral and Intraventricular Haemorrhage

The incidence of severe intracerebral haemorrhage (grades III to IV; Papile et al.[51]) was similar in untreated infants or those treated with PLS (23 *vs* 26%; Collaborative European Multicenter Study Group[26] and in infants treated with single or multiple doses of the surfactant[41] and those receiving rescue therapy, or single dose prophylaxis.[49]

The risk of cerebral haemorrhage may be increased following surfactant replacement therapy due to a fluctuating pattern of cerebral blood flow velocity (possibly resulting from a mismatch between blood gas changes and ventilator settings). Although no increase in the incidence of cerebral haemorrhage has been associated with PLS administration in large multicentre clinical trials, there have been reports of fluctuations in cerebral blood flow velocity[53,54] and cerebral blood flow volume in infants.[55,56] Further studies are clearly required to investigate the effects of surfactant replacement therapy on cerebral haemodynamics.

The incidence of intraventricular haemorrhage in infants treated with PLS was significantly lower than in untreated controls [2/14 (14%) *vs* 13/15 (87%)] in a single small study,[42] additionally, PLS administration to infants with moderate disease appeared to reduce the incidence of severe intraventricular haemorrhage compared with no treatment or treatment once the disease became severe (7 *vs* 18%; $p < 0.05$).[29]

4.4 Other Complications

PLS did not appear to significantly increase the incidence of other complications associated with prematurity or respiratory distress syndrome, including retinopathy of prematurity,[57] pneumonia, septicaemia and necrotising enterocolitis (table V). Unlike colfosceril palmitate,[1] there have been no reports to date of an increased incidence of apnoea of prematurity or pulmonary haemorrhage following PLS administration.

4.5 Long Term Clinical Tolerability

Pulmonary function (functional residual capacity, dynamic lung compliance and total pulmonary resistance) at 1 year of age in infants treated with PLS at birth was similar to that in untreated infants.[58]

The results of a 2-year follow-up of infants enrolled in the European multicentre study[26] found no significant difference between infants treated with PLS or untreated controls with regard to physical growth, the prevalence of persistent respiratory symptoms and the occurrence of major or minor disability.[39] Serum antibodies recognising

PLS and surfactant-antisurfactant immune complexes were detected in both treated and control infants indicating that immunological sensitisation to surfactant is similar in surviving treated and control infants and does not appear to be harmful over a 2-year period. However, the longer term implications are as yet unknown, and prospective follow-up of survivors is essential (for a review see Strayer[19]).

5. Dosage and Administration

PLS is administered intratracheally as a single bolus over a few seconds [concentration 80 mg/ml; smallest volume 1.25ml (100 mg/kg dose) or 2.5ml (200 mg/kg)]. In premature infants (birthweight 700 to 2000g) with established respiratory distress syndrome, rescue treatment is initiated with a single 100 or 200 mg/kg dose. Re-treatment with a single dose of 100 mg/kg is recommended in infants with an FiO_2 above 0.40 after 12 hours, and a further 100 mg/kg dose may be given 12 hours later if FiO_2 remains above 0.40.

PLS prophylaxis (single 100 or 200 mg/kg dose) may be administered within 10 minutes of birth to infants at high risk of developing respiratory distress syndrome.

6. Place of Porcine-Derived Lung Surfactant in Therapy

Surfactant replacement therapy is established for the effective treatment and prophylaxis of neonatal respiratory distress syndrome, improving the clinical outcome in premature infants who constitute a high-risk patient population.

Administration of PLS reduced the mortality rate with or without bronchopulmonary dysplasia and decreased the incidence of pulmonary air leak events, which can occur secondary to prolonged mechanical ventilation, in infants with respiratory distress syndrome (birthweight 700 to 2000g).

The optimal dosage regimen appears to be a single 100 or 200 mg/kg dose administered within 15 hours of birth, with additional 100 mg/kg doses at 12-hour intervals as required.

It remains to be determined whether PLS is beneficial in very low birthweight infants (<26 weeks' gestation and <700g birthweight) who have an increased risk of death from other conditions related to prematurity besides respiratory distress syndrome.

Pharmacoeconomic data show that surfactant replacement therapy in infants with established respiratory distress syndrome is cost effective due to its large impact on survival.[59-61] Although therapy incurs increased costs to neonatal care units, this may be offset by significant cost savings resulting from reduced disease severity and consequently reduced hospital stay, or earlier discharge to peripheral hospitals for infants > 1000g birthweight. However, it is still unclear whether there is actually a cost saving due to a reduction in the use of services.

Studies of the relative clinical benefits of PLS prophylaxis at birth compared with treatment of established respiratory distress syndrome have not uniformly documented a preferred approach, but indicate that prophylaxis may be most beneficial. Routine surfactant prophylaxis at birth for all infants born at <30 weeks' gestation results in the unnecessary treatment of 37 to 54% of infants and significantly increases the cost of neonatal care.[12] A recent cost analysis found that prophylaxis in infants born at ≤30 weeks' gestation was cost effective, whereas treatment of infants >30 weeks' gestation increased costs, with marginal clinical benefit compared with rescue therapy.[62]

It remains to be proven whether natural surfactants such as PLS have any advantages over synthetic surfactants in terms of both efficacy and tolerability. Natural surfactants appear to have a faster onset of action initially, improving gas exchange and consequently the severity of respiratory distress syndrome more rapidly than synthetic surfactants.[63-65] Although clinical outcome was similar in both treatment groups in these studies, Segerer et al.[15] found a correlation between short term response and prognosis, with infants showing rapid acute gas exchange responses after PLS having an

increased survival rate. This may have important clinical implications and requires confirmation.

PLS has been well tolerated in multicentre studies and does not appear to increase the incidence of complications associated with prematurity or respiratory distress syndrome, or to adversely affect development outcome at 2-year follow-up. Further investigation of its effects on cerebral haemodynamics is warranted, as is continued assessment of its effects on longer term (>2 years) development in infants who survive respiratory distress syndrome. Although direct comparative trials with other surfactant preparations are lacking at present, the absence of an increased incidence of complications with PLS is noteworthy, since a synthetic surfactant preparation has been associated with an increased incidence of apnoea of prematurity and pulmonary haemorrhage (reviewed by Dechant & Faulds[1]).

In addition, the lower volume in which PLS is administered (1.25 or 2.5 ml/kg) compared with other surfactants (usually 4 to 5 ml/kg) may be advantageous in improving the clinical tolerability to surfactant instillation, which can cause complications such as hypoxia, hyperoxia or airway obstruction.

Thus, while comparative trials are warranted to determine the efficacy and clinical tolerability of PLS relative to that of other currently available synthetic and natural surfactants, it is clear that PLS is a valuable drug for the treatment or prophylaxis of neonatal respiratory distress syndrome, and may ultimately prove to have some advantages over synthetic preparations.

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