REVIEW ARTICLE

Infasurf and Curosurf: Theoretical and Practical Considerations with New Surfactants

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Type II pneumocytes, normally responsible for surfactant production and release, are insufficiently formed and differentiated in the premature infant born before 34 weeks' gestation. Without an adequate amount of pulmonary surfactant, alveolar surface tension increases, leading to collapse and decreased lung compliance. Pulmonary surfactants are naturally occurring substances made of lipids and proteins. They lower surface tension at the interface between the air in the lungs, specifically at the alveoli, and the blood in the capillaries. This review examines the relative benefits of the two most recently marketed surfactants, calfactan (Infasurf) and poractant alfa (Curosurf).

Keywords: surfactant, calfactan, poractant, beractant

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Abbreviations

CLSE	Calf lung surfactant extract
DPPC	Dipalmitoyl phosphatidylcholine
NNT	Number Needed to Treat
SP-A	Surfactant apoprotein A
SP-B	Surfactant apoprotein B
SP-C	Surfactant apoprotein C
SP-D	Surfactant apoprotein D

INTRODUCTION

Pulmonary surfactants are naturally occurring substances, which are composed of lipids and proteins. They lower surface tension at the interface between the air in the lungs, specifically at the alveoli, and the blood in the capillaries. Type II pneumocytes, normally responsible for surfactant production and release, are insufficiently formed and differentiated in the premature infant born before 34 weeks' gestation. With-

out an adequate amount of pulmonary surfactant, alveolar surface tension increases, leading to collapse and decreased lung compliance.¹ A condition of surfactant deficiency gives rise to the clinical syndrome of neonatal Respiratory Distress Syndrome (RDS). A brief overview of RDS is provided below. For a more detailed discussion of RDS, the reader is referred to several recent reviews.^{2,3}

RDS occurs primarily in preterm infants < 35 weeks' gestation. The incidence progressively increases as gestational age declines. The 1999 annual report of the Vermont Oxford Network documented 27,000 neonates <1500 grams birthweight, noting a 44% incidence of RDS at birthweights of 1400–1500 grams and a gradual increase in incidence to 80% in newborns weighing <1000 grams.⁴

The typical neonate with RDS presents with increasing respiratory effort manifested by tachypnea, grunting, retractions, cyanosis and increasing oxygen requirements. Characteristic radiographic changes of the lungs are described as having a reticulogranular or ground glass appearance with air bronchograms.^{1,5}

Several clinical conditions cause surfactant

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inactivation, which present similarly to surfactant-deficient RDS. Some the similar conditions include meconium aspiration syndrome,⁶⁻⁸ early-onset group B *streptococcal pneumonia*⁹ and acute respiratory distress syndrome in patients of any age.¹⁰⁻¹² Surfactant use and efficacy in these diseases is controversial and considered largely investigational at this time; hence, these indications should not be used for formulary consideration. A summary of the available surfactants and their contents are listed in Table 1.

The purpose of this review is to examine the relative benefits of the two most recently marketed surfactants, calfactan (Infasurf, Forest Pharmaceuticals, Inc, St. Louis, MO) and poractant alfa (Curosurf, DEY, Napa, CA).

SURFACTANT EFFICACY: SHORT- AND LONG-TERM OUTCOMES

Various perinatal and postnatal events can affect the incidence and severity of RDS as well as the efficacy of surfactant replacement therapy.¹³ For example, disease severity and surfactant response may be worsened by concurrent conditions such as asphyxia, infection or meconium aspiration. Conversely, antenatal corticosteroid use and intrauterine stress reduce the risk and severity of RDS. Clinical endpoints of effi-

cacy and toxicity vary widely throughout the literature. Incidents of pneumothorax, patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), broncopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), pulmonary interstitial emphysema, necrotizing enterocolitis (NEC), neonatal mortality, mortality prior to discharge, and the combined endpoint of mortality plus BPD are commonly evaluated. Definitions of immediate clinical response and toxicity, as well as pulmonary and neurologic morbidity also vary widely.

In 1991, Hennes and colleagues published a meta-analysis of seven trials using one dose of either bovine (6 trials) or porcine (1 trial) surfactant extract for RDS.¹⁴ Only randomized controlled trials of single dose surfactant given within the first 24 hours of life were included. Of the five outcome measures evaluated (mortality, PDA, pneumothorax, IVH and BPD), only the incidents of mortality and pneumothorax resulted in a statistically significant reduction with the use of surfactant.

Jobe reported the results from four meta-analyses evaluating the effects of natural versus synthetic surfactants administered as RDS prophylaxis or treatment.¹⁵ Both types of surfactants significantly reduced the risks of neonatal mortality and pneumothoraces regardless of the tim-

Table 1. Exogenous Surfactants - Characteristics and Dosing

	Surfactant Generic (Brand)	Source	Lipid Component	Protein Component (%)	Phospholipid Concentration (mg/mL)	Dose 1 mg/kg (mL/kg)	Doses 2-4 mg/kg
Synthetic	ALEC (Pumactant) ^a	Synthetic	DPPC*, PG†	None	100	100 (1)	100
	Colfosceril palmitate (Exosurf Neonatal) ^b	Synthetic	DPPC*, PG†, tyloxapol, hexadecanol	None	13.5	67.5 (5)	67.5
Human	Human	Amniotic fluid of mature infant	Surfactant lipids	SP-A SP-B SP-C SP-D (2-5%)	20	60 (3)	60
	SF-R11 (Alveofact) ^c	Lipid extract of cow lung lavage	DPPC*, PG†	SP-B SP-C (>1.5%)	45	50 (1.1)	50
Natural	Beractant (Survanta) ^d	Lipid extract of cow lung lavage	Lung lipids, DPPC*, TP‡, PA§	SP-B SP-C (<0.25%)	25	100 (4)	100
	Calfactant/CLSE (Infasurf) ^e	Lipid extract of calf lung lavage	Surfactant lipids	SP-B SP-C (2%)	35	100 (3)	100
	Poractant alfa (Curosurf)	Organic solvent of pig lung purified by chromatography	DPPC*, PG†	SP-B SP-C (<0.25%)	80	200 (2.5)	100
	Surfactant-TA (Surfacten) ^g	Lipid extract of cow lung	Lung lipids, DPPC*, TP‡, PA§	SP-B SP-C	30	100 (3.3)	100

*= Dipalmitoyl Phosphatidylcholine; †= phosphatidylglycerol; ‡= palmitic acid; §= tripalmitin; a=Britania; b= Burroughs Wellcome; c= Boehringer; d= Abbott Laboratories; e= Forest Pharmaceuticals Inc.; f= Chiesi Farmaceutici; g= Tokyo-Tanabe

ing of administration. Notable points of this paper include recognition that surfactant replacement therapy for RDS is efficacious whether given as prophylaxis or treatment and that natural surfactants appear to work better than their synthetic counterparts.

The 1997 meta-analysis by the Cochrane Collaboration examined the benefits of prophylactic natural surfactant.¹⁶ Respiratory status improved, and the risk of RDS was decreased in all of the included trials. The following outcome measures were evaluated: pneumothorax, pulmonary interstitial emphysema, PDA, NEC, IVH, BPD, ROP, neonatal mortality, mortality prior to hospital discharge, and the combined incidence of BPD or death. Infants born at less than 30 weeks' gestation treated with prophylactic surfactant were significantly less likely to experience RDS complications such as: pneumothorax (95% CI=0.26, 0.49), pulmonary interstitial emphysema (95% CI=0.35, 0.6), neonatal mortality (95% CI=0.44, 0.83) and BPD or death (95% CI=0.75, 0.93). This analysis suggests that for every 100 infants < 30 weeks gestational age who are prophylactically treated at birth with natural surfactant, 15 pneumothoraces, 19 cases of pulmonary interstitial emphysema, and 7 neonatal deaths will be avoided.

In 1997, the Cochrane Neonatal Database published a meta-analysis comparing prophylactic surfactant administration to surfactant treatment of established RDS.¹⁷ Outcome measures evaluated in infants < 30–32 weeks gestational age were as follows: pneumothorax, PDA, IVH, BPD, ROP, pulmonary interstitial emphysema, NEC, neonatal mortality, mortality prior to discharge, and the combined endpoint of mortality plus BPD. Initial improvement in respiratory status with a decreased incidence of RDS was noted in the majority of infants receiving surfactant as prophylaxis. A decreased incidence of RDS, pneumothorax, pulmonary interstitial emphysema, mortality and BPD or death was found to be associated with prophylactically administered surfactant. In terms of numbers needed to treat (NNT), the meta-analysis suggests that for every 100 infants of <30–32 weeks gestational age treated with prophylactic surfactant, two pneumothoraces and five deaths would be prevented. These findings support the recommendation that prophylaxis should be given to all eligible neonates in this population. One caveat must be kept

in mind - as the use of antenatal corticosteroids increases, prophylactic surfactant may not have such a dramatic impact on the severity and incidence of RDS.¹⁷

ADVERSE EFFECTS

Observation of adverse events and their definitions vary significantly among studies and appear to depend on how diligent the investigators attempted to identify these problems. The most common events reported in the package inserts by the manufacturers of the three available surfactants include: cyanosis and oxygen desaturation, airway obstruction, apnea, transient bradycardia, hypotension, and reflux of surfactant in the endotracheal tube (ETT).¹⁸⁻²⁰

These events were noted to be generally transient. Surfactant reflux in the ETT tube after rapid bolus administration has led to acute airway obstruction and subsequent decreased arterial saturation and bradycardia.²¹ Other adverse events less conclusively attributed to surfactant administration include intracranial hemorrhage, PDA, pulmonary air leak, and pulmonary hemorrhage. In general, available follow-up studies of infants treated with surfactant in the neonatal period have not shown overt adverse effects.^{22,23} Reports tend to be relatively short-term and in small, isolated cohorts of children, leaving them with insufficient power to detect subtle differences in long-term neurologic and respiratory sequelae should these exist. In addition, researchers' definitions of "impairment" vary. Most importantly, surfactant therapy decreased RDS-related mortality; therefore, we cannot be certain that adverse outcomes are not simply related to the inherent increase in survival.

To date, no allergic or immunological reactions have been reported with any of the available surfactant preparations.²² Whitsett tested serum from premature infants treated with either single- or multiple-doses of beractant for antibodies to surfactant apoprotein B (SP-B) and surfactant apoprotein C (SP-C).²⁴ Beractant is a modified natural surfactant. Serum evaluations were performed at the time of treatment, then at 1 week, 4 weeks, and 6 months. Samples (n=987) from 404 neonates treated with a single dose and 2743 samples from 1024 neonates treated with multiple doses were analyzed. No IgG or IgM surfactant protein-specific antibodies were de-

tected. Even if exogenous surfactants sensitized the immune system, chances are that the individual will not need to be retreated in his or her lifetime. Furthermore, the fact that allergic responses wane with time minimizes the risk of a clinically significant allergic response later in life.

CHEMISTRY

Endogenous human surfactant is comprised of approximately 80% phospholipids, 13% neutral lipids, and 17% proteins by weight. More than 80% of the major phospholipids are dipalmitoyl phosphatidylcholine (DPPC).^{13,25,26} The chemical structure contains hydrophobic and hydrophilic chains that are tightly packed to form a monolayer at the air-liquid interface that decreases the surface tension and resists alveolar collapse.^{13,17,26,27} To date, four surfactant apoproteins have been identified (i.e., SP-A, SP-B, SP-C, and SP-D).

PHARMACOLOGY

Surfactant Synthesis

Preterm neonates with RDS have a surfactant pool size of about 5 mg lipid/kg body weight, which is approximately 1/5 to 1/10 that seen in term infants.^{25,28} Therefore, a 100 mg/kg bolus of exogenous surfactant will increase the surfactant pool size to that of a term newborn's level.²⁸ Surfactant, specifically phosphatidylcholine, is synthesized in the alveolar type II epithelial cell and subsequently stored in the lamellar bodies.^{26,28} The activities of enzymes involved in the synthesis of surfactant depend on the lung maturity of the newborn; they increase with advancing gestational age, especially toward the end of the last trimester of pregnancy.^{25,28}

Surfactant Secretion

Surfactant secretion via exocytosis from the lamellar bodies is affected by the mode of ventilation and the labor process.²⁵ Catecholamines that activate protein kinase during labor, stimulate phospholipid secretion by type II pneumocytes.²⁵ Once excreted from the lamellar bodies, the surfactant undergoes structural reorganization to form tubular myelin and subsequently a phospholipid monolayer at the air-liquid interface.^{25,28} Significant secretion of surfactant occurs after approximately 35 weeks' gesta-

tion and peaks several hours after delivery.²⁹ Among many pharmacologic agents that have been shown to increase the secretion of surfactant, antenatal administration of glucocorticoids has been extensively studied and shown to reduce the incidence of RDS in preterm infants.^{17,25,28,30,31} Glucocorticoids accelerate lung maturation via increasing phosphatidylcholine production, which in turn promote surfactant synthesis.^{25,28,30}

Mechanical factors, such as lung inflation and hyperventilation, stimulate surfactant secretion as well.²⁷ Administration of exogenous surfactant does not trigger the anticipated negative feedback of endogenous surfactant synthesis and secretion. In fact, exogenous surfactant stimulates the synthesis of endogenous surfactant in neonates with RDS.^{32,33}

SURFACTANT PROTEIN EFFECTS

Surfactant apoproteins

Hydrophilic apoprotein SP-A is thought to be involved in the regulation of surfactant turnover, the formation of tubular myelin, and immune regulation within the lung.^{28,33,34} Hydrophobic apoprotein SP-B plays a critical role in lowering surface tension and facilitating surface adsorption.³³⁻³⁶ Rider et al. demonstrated that adding SP-B to natural surfactant lipids improved the effectiveness of the surfactant to the level of natural sheep surfactant in preterm rabbits who were ventilated with positive end expiratory pressure.³⁷ In addition, SP-B increases the lateral stability of the phospholipid bilayer and provides resistance to surface tension by increasing the inter- and intra-molecular orientation of the phospholipid bilayer.^{34,38-40} The SP-B content in the various surfactant preparations appears to be a major contributor to their relative activity, duration of effect and resistance of surfactant to inactivation.^{33,34,41,42}

Hydrophobic surfactant apoprotein C (SP-C) shares similar pharmacologic characteristics with SP-B in spreadability and surface activity; however, in animal models, SP-C by itself does not improve dynamic lung compliance to the same extent as SP-B.²⁶ Currently, the function of hydrophilic surfactant apoprotein D (SP-D) is not well understood. Mice whose surfactant lacks SP-D had an increase in alveolar macrophages, which suggested that SP-D may have a role in

lung defense mechanisms.^{13,28,33}

Dipalmitoyl phosphatidylcholine (DPPC)

DPPC by itself does not have effective spreadability activity at the air-liquid interface at body temperature.^{17,35} Only with the supplementation of SP-B and SP-C does the surfactant provide its effective surface tension lowering and adsorption characteristics.^{35,43}

PHARMACOKINETICS

Administration/Delivery

Three different techniques have been used in routine clinical practice for surfactant administration.^{17,21,44} The first two approaches involve rapid infusion or slow instillation of small boluses intratracheally, both via the side port of the ETT. In the third method, surfactant is administered by nebulization. It is believed that rapid administration of relatively large volumes achieves a more uniform distribution.⁴⁵ This method may acutely increase or decrease cerebral blood flow velocity, which predisposes neonates to IVH.^{17,45,46} However, fluctuation in cerebral blood flow velocity was found to be transient.⁴⁶ Surfactant can also be nebulized.

This method provides less surfactant bioavailability, but theoretically may offer a more even distribution across an aerated lung field.¹³ However, two independent studies found that aerosolized administration of surfactant distributed non-uniformly and may result in areas of over- and under-inflation.^{28,36} Uneven areas of alveolar collapse and resistance seen in RDS and acute respiratory distress syndrome may cause aerosol to be delivered to less affected areas with consequent overdistention. Nebulization efficiency depends on the components and the chemical characteristics of the surfactants. High protein and phospholipid contents in a surfactant may reduce nebulization efficiency.⁴⁵ Surfactants with high viscosity may interfere with successful delivery secondary to cessation of aerosolization.^{44,45}

Distribution

Exogenous surfactants have typically been administered in four equally divided aliquots with the infant's position being shifted after each aliquot. A more simplified procedure with half of the surfactant dose given in the left lateral po-

sition and the rest given in the right lateral position gives similar distribution.⁴⁴ Slow infusion of surfactant results in extremely uneven distribution.⁴⁷ When given intra-tracheally as a single bolus without positional changes, the surfactant distributes quickly into all areas of the lungs within 20 seconds.⁴⁸

Metabolism/Clearance.

Type II pneumocyte reuptake is the major route of clearance and catabolism.^{33,49} Less than 10% of both endogenous and exogenous surfactants are cleared by the airway. The same amount of surfactant is taken up by alveolar macrophages. It has been reported that up to 90% of phospholipids may be reutilized or recycled over several days. Exogenous phospholipid byproducts in the type II pneumocytes may be reutilized for further synthesis.^{33,49}

Surfactant Interactions

As mentioned earlier, surfactant effectiveness is affected by many factors and concurrent conditions including protein inhibition, air leak syndrome, meconium aspiration, infections, and asphyxia.^{13,33,41}

Corticosteroids have been extensively studied for their beneficial effect on lung maturation. Neonates whose mothers received antenatal corticosteroid required less surfactant and supplemental FiO₂. Corticosteroids have been shown to act synergistically with surfactant to improve lung function, structural lung maturity, and hemodynamic stability as well as to increase endogenous surfactant synthesis.^{13,17,25,28,30,31,33} Antenatal corticosteroids decreased the severity and total incidence of RDS in infants from 28 to 32 weeks' gestational age who received one dose of prophylactic exogenous calf lung surfactant extract compared to those who did not (0% vs. 25.3%, $P < 0.05$ and 12.5% vs. 39.8%, $P < 0.05$, respectively).⁵⁰ Further analysis of data on infants <28 weeks' gestation showed similar results.

Also, antenatal steroids reduce the rate of mortality and IVH, two major complications commonly seen in neonates in this age group. The National Health Institute Consensus Conference in 1995 recommended the use of antenatal corticosteroids in all fetuses between 24 and 34 weeks' gestation who are at risk of preterm delivery, regardless of race, gender, or availability of surfactant unless there is evidence that

adverse effects on the mother or the delivery will occur.⁵¹

NEWLY MARKETING SURFACTANTS

Several surfactant preparations have been studied in the United States and other countries. All are effective but differences exist in the surfactant source, and phospholipid and protein content for these products. In the United States, two surfactant products have been available for many years, colfosceril palmitate (Exosurf) and beractant (Survanta). The modified natural product beractant has dominated market share due to superior efficacy; however, new products must be compared with currently marketed surfactants, especially beractant. In the face of decreased market demand and the availability of better surfactant preparations, the manufacturer has ceased market production of colfosceril palmitate.

CALFACTANT (INFASURF)

Calfactant is a calf lung surfactant extract (CLSE) comprised of phospholipids, neutral lipids and hydrophobic apoproteins SP-B and SP-C. It is an off-white suspension in normal saline with no preservatives. Commercially available calfactant has a concentration of 35 mg/mL of total phospholipids (26 mg of which is phosphatidylcholine). Protein composition is approximately 2% by weight (0.65 mg/35 mg total weight), 40% of which is SP-B.¹⁹ Calfactant intratracheal suspension is supplied in a single-use 6-mL glass vial, which should be refrigerated at 2° to 8°C and be protected from light. Once opened, any unused portion should be discarded. At our institution, calfactant is contracted at the listed AWP price of \$732.12/6 mL vial.

Like human lung surfactant, CLSE exhibits rapid adsorption of phospholipids and has the highest activity in improving lung mechanics among exogenous surfactants.^{35,52-54} Hall et al. reported different rates of adsorption for various surfactants. Calf lung surfactant extract were associated with the most rapid rate of absorption, followed by natural whole calf lung surfactant, beractant, colfosceril palmitate, and DPPC alone.³⁵ When compared with natural whole calf lung surfactant, both calfactant and beractant had equivalent adsorption rate at the air-liquid in-

terface.^{35,42} Pulmonary function improvements were demonstrated by the increase in PaO₂/PAO₂ ratios, tidal volumes, minute ventilation, and ventilatory compliance. Changes in all these endpoints resulted in increased arterial oxygenation and ventilatory compliance.⁵³ Calfactant was unaffected by inhibitory protein (e.g., albumin, fibrinogen). This is a desired characteristic that may have a strong association with its selectively high content of surfactant apoprotein SP-B.

Animal Experience with Calfactant versus Placebo

Calfactant is more potent and yields a more favorable outcome than placebo and other surfactants.^{52,54,55} Cummings and colleagues performed a controlled trial in 29 preterm lambs who were deficient in surfactant.⁵² The physiologic effects of colfosceril palmitate, calfactant, and beractant were compared with natural sheep surfactant and placebo. All preterm lambs that received saline endotracheally died by 9 hours of age whereas 67% lambs (four of six) treated with calfactant survived at the end of 24 hours. Only two lambs from the calfactant treated group required retreatment at 12 and 15 hours of age. The initial arterial oxygenation responses were much lower ($P < 0.02$) in the saline treated group (44 ± 7 mmHg) as compared to the calfactant group (290 ± 33 mmHg). Similar improvements were observed in the comparison of ventilator efficiency indexes used to determine lung compliance with the ratios of saline and calfactant groups being 0.022 ± 0.003 mL/kg/cm H₂O and 0.140 ± 0.014 mL/kg/cm H₂O, respectively ($P < 0.02$). The responses in the calfactant treated group remained relatively unchanged at the end of 12 hours. The rate of change for oxygenation was -2 ± 5 mmHg/hour and the ventilator efficiency index was 0 ± 0.002 mmHg/hour. Although this study involved a small number of animals, its findings showed that calfactant treated lambs had favorable outcomes compared with placebo.

When compared with other surfactants, calfactant had a longer duration of effect that allowed for less frequent dosing. Initial arterial oxygenation was highest in the calfactant and natural sheep surfactant groups; however, the effect deteriorated dramatically in the natural sheep surfactant group over the first 12 hours

whereas it was sustained in the calfactant group (rate of change w/calfactant -2 ± 5 mmHg/hour vs. natural sheep surfactant -24 ± 6 mmHg/hour, $P < 0.02$). Both the colfosceril palmitate and beractant groups had much lower initial response. Similar results were observed when $\text{PaO}_2/\text{PAO}_2$ ratios were compared between groups. Improved oxygenation and ventilation was highest and only sustained in calfactant group. Survival was improved in natural sheep surfactant, beractant, and calfactant groups compared with colfosceril palmitate and control groups ($P < 0.01$). Only calfactant-treated lambs had significant survival improvement when compared with natural sheep surfactant-treated lambs ($P < 0.02$). This suggests that human trials should monitor closely for faster and greater clinical responses with calfactant than beractant, and ventilator management strategies should anticipate earlier, more rapid weaning with calfactant to avoid overventilation with associated risks for pneumothorax and IVH.

Calfactant versus Placebo

Kwong et al. conducted a study using CLSE for the prevention of hyaline membrane disease in 24 to 28 weeks' gestational-age infants.⁴⁰ Twenty-seven newborns, 14 in the CLSE group, and 13 in the saline group were included. Upon intubation, each neonate in the CLSE group received 3 mL of CLSE (30 mg/mL) followed by 7 mL of air via the ETT. Patients in the saline group were given 3 mL of saline using the same procedure. After being stabilized in the delivery room, all infants were transferred to the neonatal intensive care unit (NICU) and followed by usual attending neonatologists and staff. Usual unit protocols and policies were observed in all infants. Initial FiO_2 in the group receiving CLSE (0.44: range=0.40–0.48) was significantly lower ($P < 0.001$) than that of saline-treated group (0.59: range=0.55–0.64). There was a significant difference ($P < 0.001$) in mean airway pressure in those receiving CLSE (6.8: range=5.7–7.9) and those given saline (9.4: range=8.8–10). Consistent with animal studies, ventilator efficiency index was higher in CLSE treated group than saline group, 0.48 (0.37–0.59) mL/kg/mmHg and 0.33 (0.27–0.38) mL/kg/mmHg, respectively ($P = 0.01$). All responses were sustained and remained unchanged at 48 hours of life in both groups. Incidences of major complications such as intracra-

nial hemorrhage and air leak syndrome were not detectably different between groups.

Prophylaxis versus Rescue

Several studies have examined the optimal time to administer exogenous surfactant to preterm neonates in order to achieve maximal response. Prophylactic use of surfactant in very premature infants (< 30 weeks gestational age) has shown significant benefits compared to rescue treatment.^{21,39,55–58}

Prophylactic strategy of surfactant administration has clinical advantages and disadvantages. This strategy delivers surfactant to the alveoli before the initiation of mechanical ventilation and/or the first breath of life and any possible barotrauma or lung injury.⁵⁷ It may be more evenly distributed when given at birth while liquid absorption in the lungs is occurring. A 1998 Cochrane review reported an overall 40% reduction in risk of mortality when infants < 32 weeks gestational age are treated with exogenous surfactant within 15 minutes of birth compared with those treated a few hours later.¹⁷ This meta-analysis showed a significant reduction in the risk of pneumothorax, pulmonary interstitial emphysema, BPD or death in infants < 30 weeks' gestation in patients treated prophylactically (overall risk reduction 38%, 46%, and 27% corresponding to NNT of 50, 33, 17, respectively, to prevent one event of the above complications).

Several concerns surround the prophylactic use of surfactant. These include technical difficulty of administration (i.e., surfactant being administered before the infants are stabilized and before the position of the ETT can be verified) and unnecessary use in infants who would not develop RDS.^{56,57,59} Different outcomes regarding the benefits of prophylaxis have been reported in several available clinical trials. Dunn et al. reported no benefit in either gas exchange or complications of prematurity following prophylactic use of bovine surfactant extract in 182 neonates < 30 weeks gestational age.⁵⁹ However, it should be noted that almost 50% of newborns randomized to receive surfactant as rescue therapy were clinically surfactant-sufficient and thus may have skewed the results. Because separate data and analysis were not reported for those who developed RDS, it is impossible to demonstrate whether prophylactic use was beneficial for this age group.

In a comparative trial using CLSE as immediate prophylaxis and rescue therapy in 479 preterm infants, Kendig and colleagues reported a lower incidence of pneumothoraces in the prophylaxis group.⁵⁷ This difference reached statistical significance when the subgroups of <26 weeks' gestation were examined; 6/85 (7%) prophylaxis group vs. 13/72 (18%) rescue group, ($P=0.03$; NNT=9). A significantly higher survival rate ($P=0.028$; NNT=13) was also observed in the prophylaxis group (206/235; 88%) compared to those receiving rescue therapy (195/244; 80%). Brown et al. compared the efficacy of prophylaxis and rescue strategies using beractant and calfactant in a retrospective cohort of 1097 neonates from 12 centers who had birth weights <1251 grams and gestational age <30 weeks.⁵⁶ They reported a significantly higher survival rate ($P<0.05$, NNT=5) in neonates with birth weights <750 grams receiving prophylaxis than those receiving rescue therapy, 83/127 (65%) vs. 95/222 (43%), respectively. In a larger retrospective study involving 1248 infants 29 to 32 weeks of gestation, Kattwinkel et al. observed similar favorable outcomes associated with prophylaxis strategy using calfactant.³⁹ Although significant differences were not seen in certain subgroups of different birth weights and gestational ages, overall results showed a significantly lower mortality rate in those receiving prophylaxis therapy. There was a significant difference in mortality ($P=0.033$; NNT=77) when those receiving prophylaxis (3/267; 0.5%) were compared to the rescue group (11/621; 1.8%). Likewise there was a significant difference ($P=0.014$, NNT=25) in the need for oxygen supplementation at 28 days of life when the prophylaxis group (32/627; 5%) was compared to the rescue group (54/621; 9%).

Prophylactic administration of exogenous surfactant also allows for early mechanical ventilation weaning to nasal CPAP, which would minimize ventilation-induced complications and decrease cost of care.⁶⁰ The 1999 Vermont Oxford Network reported greater than 80% of infants at birthweights less than or equal to 1000g developed RDS and more than 70% of them received exogenous surfactants.⁴ Considering clinical advantages and disadvantages of prophylactic strategy, it is recommended that prophylactic use of surfactant be reserved for infants at greater risk for RDS, such as those ≤ 30 weeks' gestation.^{56,57,59} When a prophylaxis strategy is used

to facilitate extubation to nasal CPAP, it stands to reason that surfactants that are more potent and longer acting (e.g., calfactant) may be superior to beractant, although this remains to be proven.

Single-dose versus Multiple-dose

Dunn et al. studied the need for surfactant redosing using bovine surfactant extract in 75 newborns from 30 to 36 weeks gestation.⁶¹ Patients were randomly allocated to one of three groups: control, single-dose surfactant, and multiple-dose surfactant. Those enrolled were further stratified by gestational age (30–33 weeks and 34–36 weeks) and antenatal steroid exposure. Surfactant was instilled intratracheally at around 4 hours of life. It is unclear how many newborns in the multiple-dose group received the second dose of surfactant within 12 hours of the initial dose. Marked initial oxygenation response was seen in the surfactant treated groups within 10 minutes after instillation, and it persisted until 12 hours afterwards. Sixteen (67%) of 24 infants in the single-dose group and 23 (85%) of 27 infants in the multiple-dose group were adequately oxygenated at 0.21 FiO₂ during the first 10 minutes. By 12 hours of life, 88% of the single-dose group and 96% of the multiple-dose group required room air. Only infants in the multiple-dose group showed sustained benefits of surfactant, as measured by improved FiO₂ ($P<0.05$) and ventilation index ($P<0.01$), until 72 hours of life. However, no significant differences were observed in long-term outcomes such as duration of positive pressure ventilation, duration of oxygen therapy, and death as well as complications of prematurity. Considering the small number of patients enrolled in this study, it is likely that there was not sufficient power to detect modest differences.

The authors suggested that although multiple-dose surfactant therapy did not offer long-term benefits, it might reduce the severity of disease. Noteworthy is the fact that infants included in this study were >30 weeks gestational age, a group whose susceptibility to RDS has changed considerably over the last decade due to increased use of antenatal corticosteroids and better ventilatory management. Furthermore, this study was intended to evaluate short-term gas exchange, morbidity and clinical course only. The authors failed to provide details of respiratory management beyond the

first few days. Although the incidences of PDA, IVH, and air leak syndrome were similar in both groups, other confounders such as infection rates, pulmonary hemorrhage, NEC, and persistent pulmonary hypertension were not reported.

Calfactant versus Colfosceril palmitate

Hudak et al. conducted two multicenter, randomized comparison trials of colfosceril palmitate versus calfactant for the treatment and the prevention of neonatal RDS.^{54,62} The treatment trial involved 21 NICU and 1033 infants with clinically confirmed RDS.⁶² Calfactant-treated neonates had a lower average FiO_2 (0.47 ± 0.01 vs. 0.39 ± 0.01 ; $P < 0.0001$) and MAP (8.6 ± 0.1 cmH_2O vs. 7.2 ± 0.1 cmH_2O ; $P < 0.0001$) throughout 72 hours of life after the initial surfactant dose. In terms of complications, the calfactant treated group showed a 47% reduction in the incidence of total early (≤ 7 days of life) air leak (20.9% vs. 10.7%), 53% reduction in pulmonary interstitial emphysema (16.1 vs. 7.2%), and 39% reduction in pneumothorax (8.7% vs. 5.0%). Significant long-term benefits were also observed in calfactant-treated infants. They had significantly reduced days of assisted ventilation (5.4 vs. 4.4; $P = 0.0006$), days requiring $> 21\%$ oxygen (9.0 vs. 7.7; $P = 0.04$), and days of positive pressure support (6.9 vs. 5.8; $P = 0.03$). There was also no difference in mortality rate for RDS-related death: 4.4% calfactant vs. 4.1% colfosceril palmitate, 95% CI=0.72, 2.32; and respiratory-related death: 6.3% calfactant vs. 6.7% colfosceril palmitate, 95%

CI=0.65, 1.63. This lack of significance may be due to insufficient power. Findings of this study confirmed the superior benefits of calfactant therapy over colfosceril palmitate in reducing severe complications seen with RDS (e.g., air leak syndrome and pulmonary interstitial emphysema). The results of this trial and the number of patients needed to prevent one event of each complication are listed in Table 2. Although other demographic data and respiratory measurements at entry were similar in both groups, gestational age was statistically greater ($P = 0.04$) in the calfactant group (31 ± 3.5 weeks) compared to those receiving colfosceril palmitate (30.5 ± 3.4 weeks), a factor that may have affected lung function and treatment outcomes.

The neonatal RDS prevention trial was conducted at 10 NICUs and enrolled 846 newborn infants < 29 weeks' gestation.⁵⁴ Colfosceril palmitate was associated with less favorable outcomes than calfactant. This was true for RDS-associated endpoints (i.e., FiO_2 and mean airway pressure) and complications including air leak syndrome, pulmonary interstitial emphysema, and pneumothoraces. Calfactant-treated infants, who received the same number of doses as those in the colfosceril palmitate group, required significantly lower FiO_2 (0.42 ± 0.01 vs. 0.33 ± 0.01 , $P < 0.0001$) and mean airway pressure (7.1 ± 0.2 vs. 6.0 ± 0.1 cmH_2O , $P < 0.0001$) from 1 to 72 hours of life. These benefits were not seen in colfosceril palmitate group until 6 hours of life. The calfactant-treated group showed a 45% reduction in the incidence of total early (≤ 7 days) RDS-related air leak (14% vs. 8%), 60% reduction in pulmonary interstitial emphysema (11% vs. 5%), and 40% reduction in pneumothorax (6% vs. 4%). This study reported a lower rate of mortality in the calfactant group at 28 days after birth (12% vs. 16%, risk ratio 0.75, 95% CI=0.54, 1.04); however, incidence of BPD and oxygen requirement at 28 days were similar in both groups (Table 2).

Of note is a significantly increased incidence of total IVH in the calfactant group (39.0% vs. 29.9%, $P = 0.005$). The incidence of severe (grade III or IV) IVH was not statistically significant (11.8% vs. 8.3%, $P = 0.09$); however, there may be insufficient power to detect this 42% increase rate. This finding could not be associated with any factors, except for the increased incidence of bradycardia, arterial desaturation, and airway obstruction during calfactant redosing. These

Table 2. Comparison trials of calfactant versus colfosceril palmitate in the prevention and treatment of neonatal RDS^{54,62}

Complication	Prevention of RDS			Treatment for RDS		
	RR	ARR	NNT	RR	ARR	NNT
Pneumothorax (≤ 7 d)	0.60	0.02	50	0.61	0.037	27
PIE (≤ 7 d)	0.40	0.06	17	0.47	0.089	11
Air leak (≤ 7 d)	0.55	0.06	17	0.53	0.010	10
IVH						
Total	1.30			1.00		
Severe (grades II & IV)	1.42			1.05		
PVL	1.97			2.54		
Mortality at 28 days	0.75	0.04	25			

Assumption made: All neonates without surfactant would have developed RDS (100% risk)

RR= Risk ratio calfactant/colfosceril palmitate; ARR= Absolute Risk Reduction for calfactant compared to colfosceril palmitate; NNT= Number of neonates needed to be treated with calfactant to avoid one episode of complication compared with colfosceril palmitate.

All complications mentioned reached statistical significance.

increased episodes may have been associated with the fact that calfactant was administered using the colfosceril palmitate protocol, which may not have been the correct method. Another finding of concern is a larger number of periventricular leukomalacia cases in the calfactant group in both prevention and treatment trials (6.5% vs. 3.3%, 95% CI=1.09, 3.8, risk ratio 1.97, 97% increase rate in the prevention trial; 3.3% vs. 1.3%, risk ratio 2.54, $P=0.015$, 154% increase rate in the treatment trial).

This increased periventricular leukomalacia incidence was best correlated with hypocarbia demonstrated by lower PaCO_2 levels observed up to 48 hours of life in the calfactant group. The authors proposed aggressive and meticulous respiratory management immediately after birth to minimize possible hypocarbic incidence resulting in decreased cerebral blood flow which predisposes infants to hypoxic-ischemic brain injury, a risk factor for periventricular leukomalacia.

Calfactant versus Beractant

Bloom et al.⁵⁵ compared calfactant to beractant in the treatment and prevention of RDS in 982 preterm infants and reported findings similar to those in the animal study by Cummings et al.⁵² Calfactant showed more pronounced initial effects after dosing than beractant.

FiO_2 change was greater after the first dose in the calfactant-treated group -0.18 ± 0.21 than in the beractant treatment group -0.13 ± 0.20 ($P < 0.01$). This study also showed that time elapsed from the previous dose to the next dose was shorter in the beractant-treated group. In the treatment arm, beractant required redosing every 9 hours on average versus every 13 hours in the calfactant group ($P=0.006$ and $P < 0.001$). In addition, more newborns in both treatment and prevention arms of the beractant group required 4 doses of surfactant, 33/305 (10.8%) vs. 22/303 (7.3%) infants in treatment arm ($P=0.002$) and 26/194 (13.4%) vs. 19/180 (10.6%) infants in prevention arm ($P=0.3$). Although effects that are more favorable were observed in calfactant group, differences in the duration of mechanical ventilation and supplemental oxygen in the treatment arm were not statistically different. However, the calfactant group in the prevention arm had shorter duration of supplemental oxygen (46 ± 48 days vs. 36 ± 39 days; $P=0.02$) and mechani-

cal ventilation (27 ± 26 days vs. 20 ± 22 days; $P=0.012$). No significant differences in major adverse effects or complications were noted.

Based on the findings presented, calfactant offers some advantages over beractant: it requires less frequent redosing and provides faster and more pronounced initial response. In terms of complications, no significant differences can be demonstrated in the incidence of survival at discharge, air leak syndrome, and IVH, the latter two being both total and severe - grades III and IV (Table 3). As the number of patients enrolled in this study exceeded the number needed to detect a 25% difference in both arms, it is reasonable to conclude that there was sufficient power to detect such difference in these complications should they have existed, but smaller differences may have been missed. Consequently, another multicenter trial is currently being initiated. This is a 2-year prospective, randomized comparison study of beractant and calfactant for the prophylactic use to prevent RDS and the treatment of established RDS in preterm infants. The anticipated number of subjects to be enrolled is approximately 4000 infants from 50 centers.

PORACTANT ALFA

Poractant alfa intratracheal suspension is a porcine-derived natural surfactant. It contains approximately 99% phospholipids and 1% SP-B and SP-C suspended in 0.9% sodium chloride solution.¹⁸ It has recently been approved for use in the United States and has been available in Europe since 1992. Currently, poractant alfa is only indicated for rescue therapy of established RDS; however, it has been proven useful for prophylaxis as well.⁶³ Poractant alfa should be stored in the refrigerator until use. According to the manufacturer, unopened, unused vials that have been warmed to room temperature can be returned to the refrigerator within 24 hours. This should not be repeated more than once. Vials are single-use only and should be protected from light. Poractant alfa is available in 1.5 and 3 mL vials. AWP for each is \$440 and \$762, respectively.

The initial dose is 2.5 mL/kg (200 mg/kg). The manufacturer recommends poractant alfa be administered via a 5 French catheter inserted into the ET tube in two aliquots while positioning the infant on either side. Repeat doses of 1.25 mL/kg (100 mg/kg) may be given at 12-hour inter-

Table 3 . Comparison of calfactant to beractant in the treatment and prevention of RDS⁵⁵

Complication	Treatment Arm			Prevention Arm		
	Calfactant (n=303)	Beractant (n= 305)	P value	Calfactant (n=180)	Beractant (n=194)	P value
Any air leak	15%	18%	0.27	13%	10%	0.41
IVH						
Grades I & II	30%	35%	0.20	37%	31%	0.13
Grades III & IV	11%	10%	0.68	5%	5%	0.82
Alive at discharge	82%	83%	0.83	86%	92%	0.06

vals if the infant still requires mechanical ventilation with supplemental oxygen. It is recommended by the manufacturer that treatment be limited to a total of 4 doses.

Poractant alfa versus Control

The Food and Drug Administration based approval of poractant alfa on two multicenter international studies.^{64,65} The first involved 8 European NICUs and compared poractant alfa with untreated controls for the treatment of established RDS.⁶⁴ The second involved 15 European NICUs and sought to determine the combined incidence of mortality and BPD associated with RDS.⁶⁵

In both trials, infants were included if they were between 700 and 2000 gram birthweight, had clinical and radiographic findings indicative of RDS, were between 2 and 15 hours of life, required mechanical ventilation with $\text{FiO}_2 \geq 0.6$, and had no other complicating disease. Seventy-seven infants were randomized to treatment with 200 mg/kg (2.5 mL/kg) single-dose poractant alfa and 69 infants were randomized to the control group. Poractant alfa was administered either as a single bolus into the lower trachea or as two doses into each bronchus. No placebo was given, but control infants were disconnected from the ventilator and manually ventilated similar to the study group.

RDS-related mortality was reduced from 51% to 31% ($P < 0.01$). This means 5 patients would need to be treated to prevent one neonatal death. Over the same time period, poractant alfa-treated infants required a median of 35% less time on mechanical ventilation and were significantly less likely to develop pulmonary interstitial emphysema and pneumothoraces. NNT with poractant alfa to prevent one pneumothorax or one case of pulmonary interstitial emphysema are 5.9 and 6.3, respectively. A 38% decreased risk of grade III-IV BPD was observed in

the surfactant group, 16% versus 26%. This difference was not statistically significant, possibly due to insufficient power. However, if this data holds up in larger studies, only 10 patients would need to be treated to prevent one case of BPD, which is clinically relevant. A 39% decrease in the combined outcome of death and or BPD was also noted in surfactant-treated neonates.

Early versus Late Treatment of Established RDS with Poractant alfa

The literature does not provide conclusive evidence as to the optimal time for administration of exogenous surfactant; however, prophylaxis and early intervention have proven to be the most beneficial. A randomized, multi-center trial compared outcomes of infants given a single dose of poractant alfa at different stages of RDS.⁶⁶ Infants with moderately severe RDS, defined as FiO_2 requirement between 0.4 and 0.59, were randomized to early single-dose treatment with poractant alfa 200 mg/kg ($n=86$) or the control group ($n=96$). The control infants were eligible to receive "late" treatment with poractant alfa provided their RDS became severe, defined as FiO_2 requirement ≥ 0.60 . Forty-nine out of 96 infants (51%) received "late" surfactant replacement, 47 infants did not receive any poractant alfa.

Several significant advantages of early treatment were noted. Grade III-IV IVH was reduced by 56% (8% vs. 18%, $P < 0.05$); 28-day mortality reduced by 61% (9 vs. 23%, $P < 0.05$) and the combined incidence of mortality and BPD reduced by 47% (18 vs. 34%, $P < 0.05$). Infants treated early had a decreased need for mechanical ventilation ($P < 0.01$) and supplemental oxygen ($P < 0.05$). No patients in the early treatment group died of respiratory failure, whereas four in the control group did.

The authors conclude that treatment with poractant alfa when RDS is moderately severe

can prevent or reverse its progression of disease in some infants. It should be mentioned that late treatment was still beneficial, as evidenced by an increase in PaO_2 , increase in $\text{PaO}_2/\text{FiO}_2$ ratio, and decrease in peak inspiratory pressure for both groups.

Prophylaxis versus Rescue with Poractant alfa

Egberts and colleagues published a meta-analysis of three poractant alfa prophylaxis trials versus treatment trials.⁶³ Three main outcome measures were evaluated: the incidence of RDS at 6 hours after birth, neonatal mortality, and chronic lung disease in survivors at 28 days post-natal age. A limitation of this study was its comparison of a single-dose poractant alfa prophylaxis with a multiple-dose regimen, since groups were not mutually exclusive. The authors define the groups as “prophylactically-treated” and “rescue-eligible.”

Mortality and the incidence of severe RDS (grade III–IV) were significantly reduced in the multiple-dose group. The combined incidence of pneumothorax plus pulmonary interstitial emphysema was also reduced in favor of the multiple-dose group. These are relevant conclusions as long as it is recognized that the paper compares single-dose prophylaxis with prophylaxis plus additional rescue doses.

Single-dose Poractant alfa versus Multiple-dose

The second trial used for FDA approval of poractant alfa involved 15 European NICUs. The primary study endpoint was the combined incidence of mortality and BPD associated with RDS.⁶⁵ Inclusion criteria were identical to the first trial.⁶⁴ Included neonates were randomized to a single- or multiple-dose replacement regimen. All babies received 200 mg/kg (2.5 mL/kg) immediately after randomization. Infants in the multiple-dose group could receive up to 2 additional 100 mg/kg (1.25 mL/kg) doses of poractant alfa at 12 and 24 hours of life if they still required mechanical ventilation with supplemental $\text{FiO}_2 > 0.21$.

One hundred and seventy six neonates received single-dose poractant alfa and 167 received additional doses. Of the 167 allowed additional doses, 58 (35%) required no doses, 42 (25%) required one, and 67 (40%) required both

additional 100 mg/kg doses. Taken altogether, 65% of babies in the multiple dose group required additional doses by study criteria. Interestingly, 68% (120/176) of those randomized to receive only the single bolus dose of poractant alfa qualified for additional rescue doses.

All patients receiving poractant alfa had rapid improvement in oxygenation (within 15 minutes of the 200 mg/kg initial bolus), which reduced their median supplemental oxygen needs from 0.85 to 0.35 in the single-dose group and from 0.90 to 0.40 in the multiple-dose group. Within 6 hours of dosing, peak inspiratory pressure and mean airway pressure could be weaned in both groups. Infants treated with additional poractant alfa doses required significantly less oxygen at 24, 48, and 72 hours of life, $P < 0.001$, $P < 0.001$, and $P < 0.05$, respectively. The main outcome variable, combined incidence of mortality, and BPD was 33% vs. 27% in favor of the multiple-dose group. Although this was not statistically significant, an insufficient sample size may have precluded the ability to detect a small difference.

Overall, 28-day mortality was significantly lower for infants given additional doses, 13 vs. 21%. Incidence of pneumothorax across the treatment groups was 18 % and 9%, in favor of the multiple-dose group ($P < 0.05$). The authors noted that 85% of babies who died as a result of respiratory failure had pneumothoraces. No significant differences were noted for the secondary endpoints: duration of mechanical ventilation, time requiring supplemental oxygen, incidences of pulmonary interstitial emphysema, pulmonary hemorrhage, intracranial hemorrhage, PDA, septicemia, or NEC. As with most trials, there are two possible reasons for a lack of statistical significance, either no difference exists or there were an insufficient number of patients in each treatment group to prove that a difference exists. Compared to the large number of patients enrolled in beractant and calfactant studies, it is likely that many of these poractant alfa trials lack the power to prove subtle differences in secondary endpoints.

Large- versus Small-Dose Treatment of RDS with Poractant alfa

The Curosurf 4 trial involved 82 hospitals in 13 European countries.⁶⁷ The main objective was to compare efficacy of two different poractant alfa

multiple-dose dosing schemes. Patients randomized to the low-dose regimen ($n=1069$) received an initial poractant alfa dose of 100 mg/kg and were eligible for up to two additional 100 mg/kg doses at 12-hour intervals if they continued to require mechanical ventilation with supplemental oxygen. The total possible cumulative dose was 300 mg/kg in up to 24 hours. Patients randomized to the larger-dose regimen ($n=1099$) initially received 200 mg/kg of poractant alfa. If they continued to require mechanical ventilation with supplemental oxygen, they were eligible for a maximum of four additional 100 mg/kg doses at 12-hour intervals over 72 hours, with a 600 mg/kg possible cumulative dose. Surfactant was administered as an intratracheal bolus. Subsequent ventilator weaning was accomplished first by lowering the FiO_2 and inspiratory time then by lowering the inspiratory pressure.

There were no differences between the large- and small-dose regimens for all three main outcome measures (i.e., death or oxygen dependence at 28 days, death before hospital discharge, death or oxygen dependence at expected date of delivery). Of the 15 secondary outcome measures, the only one reaching statistical significance was fewer days with FiO_2 requirements of > 0.40 in babies who received the high dose regimen. The sample size for this study was calculated to have 80% power to detect a 5% difference in the incidence of death or prolonged oxygen need (15% versus 20% between groups). Because this study enrolled over 2000 patients, it is likely that there was sufficient power to detect differences in these outcome measures should they have existed.

In the first 36 hours, infants receiving the larger dose regimen had improved oxygenation and gas exchange over the lower dose. Although these short-term benefits could not be correlated to improved clinical outcomes, the authors state that fewer of these infants went on to require retreatment. Indirectly, this may incur cost savings due to decreased drug acquisition, monitoring and administration costs.

Poractant alfa versus Colfosceril palmitate and Beractant

Poractant alfa has superior effects on respiratory dynamics compared to colfosceril palmitate.⁶⁸ Its more favorable pharmacodynamic profile may be largely attributed to the presence of SP-B and SP-C, which are not present in the syn-

thetic product colfosceril palmitate. In order to determine sample size, Speer et al. conducted a pilot study for a large-scale trial that would evaluate if differences between two commercially available surfactants exists.⁶⁹ Seventy-three infants with clinical and radiographic evidence of RDS were randomized between 1 and 24 hours of life to surfactant rescue treatment with poractant alfa ($n=33$) or beractant ($n=40$). Initial doses of surfactant in all newborns were given before 15 hours of life with a median age of 3 hours for both groups. Each group was allowed additional doses if required.

Poractant alfa had greater effects than beractant on measures of improved RDS. Within 5 minutes, FiO_2 was weaned for both treatment groups. FiO_2 was weaned from 0.9 to 0.34 in newborns receiving poractant alfa compared to 0.9 to 0.5 in those given beractant. Whether this was due to the larger initial poractant dose (200 mg/kg) than beractant dose (100 mg/kg) is not clear. However, the volumes of the initial doses given, 2.5 mL/kg poractant and 4 mL/kg beractant, make use of a higher initial dose feasible for poractant alfa and probably not beractant. Other markers of lung compliance (i.e., ventilator peak inspiratory pressure and mean airway pressure settings) were also significantly lower with poractant than beractant during the first 24 hours, but did not persist beyond 24 hours. The actual values for the differences in peak inspiratory pressure and mean airway pressure were not provided. Median differences appear to be approximately 2 cm H_2O lower peak inspiratory pressure and 1 cm H_2O lower mean airway pressure with poractant alfa versus beractant in the first 24 hours.

The study was too small to show outcome differences in pulmonary complications or death. The authors indicated that 708 patients would have been needed to detect a reduction in the combined endpoints of death or BPD from 25% to 15% by switching from beractant to poractant alfa. The trend toward better outcomes with poractant alfa than synthetic surfactants is supported by a comparative trial with another synthetic surfactant, pumactant.⁷⁰

This study treated 99 patients with poractant and 100 patients with pumactant before the data safety and monitoring committee closed the study due to concerns about excess pulmonary mortality with pumactant (5% for poractant vs

21 % for pumactant). Natural surfactants appear superior to synthetic surfactants.

IMPORTANCE OF INITIAL SURFACTANT EFFECT

It is estimated that up to 25% of neonates do not have an adequate respiratory response to surfactant replacement.⁷¹

It has been hypothesized that this poor initial response may be predictive of morbidity and mortality.⁷¹ Two hundred and fifty three patients from the Curosurf 4 trial who had severe RDS were evaluated. Immediate response was defined as the difference between the $\text{PaO}_2/\text{PAO}_2$ ratio immediately before and one hour after poractant alfa dosing.⁶⁷ Results showed that there was a significant correlation between a low $\text{PaO}_2/\text{PAO}_2$ ratio and an increased incidence of pneumothorax and mortality rate. It appears that early response is an important marker of outcome with surfactant therapy. Therefore, selection of surfactant doses and products with the greatest initial effects may have important clinical benefits. If so, this would favor faster acting surfactants such as calfactant and poractant over beractant.

CLINICAL TOLERABILITY AND FOLLOW-UP

The Cochrane Collaboration meta-analysis did not identify any significant adverse events that were directly correlated with exogenous surfactant administration.¹⁷ Three of the seven studies included evaluated poractant alfa. One-year follow-up of 13 infants treated with single-dose poractant alfa at birth showed no effect on pulmonary function when compared to untreated controls. It appears that infants surviving RDS treatment with poractant alfa are not at any increased risk for pulmonary dysfunction.⁷²

Forty-four infants participating in the first European multicenter trial of poractant alfa were evaluated at two years corrected age. No differences were noted in the outcome measures of growth, respiratory status, and neurodevelopment. Similar serum antibody titers were found in both surfactant-treated and control toddlers. This follow up suggests that poractant alfa treatment of RDS is not associated with an increase in 2-year morbidity.⁷³

PHARMACOECONOMICS

Cost-effectiveness evaluation of poractant alfa based on a theoretical study model for populations with a 55% incidence of RDS showed the most cost-effective treatment approach to be with prophylaxis.⁷⁴ When the incidence of RDS in a given population is less than 55%, only prophylaxis and early rescue with poractant alfa were cost-effective. As other management strategies alter the frequency and severity of RDS, economic analyses will change.

In recent years, significant advances in neonatal medicine have positively impacted the incidence and severity of RDS. Traditional pharmacoeconomic analyses do not consider the use of antenatal corticosteroids, improved ventilator management, and improved prenatal care and are therefore of limited applicability. Furthermore, the overwhelming evidence supporting decreased RDS-related morbidity and mortality with surfactant therapy ethically compels clinicians to use these pharmaceuticals regardless of cost. It, therefore, seems that pharmacoeconomic analysis of these drugs may be a moot point.

SUMMARY AND CONCLUSIONS

The first European multicenter trial of surfactant replacement with poractant alfa had a mortality rate of 31% in the poractant alfa-treated group.⁶⁴ Speer et al., using identical inclusion criteria, observed a 21% mortality rate.⁶⁵ They note that this decrease may be indicative of the "improving skills of the hospital staff" caring for these neonates. This point cannot be taken too lightly. It is of dire importance that we do not underestimate the inherent "learning curve" that comes with the introduction of new therapies in health care. The lack of appreciation and understanding of the pharmacokinetic and pharmacodynamic differences between the commercially available surfactants can greatly compromise successful implementation of treatment with more potent and faster acting surfactants. Institutions should choose a single surfactant for their formulary, avoiding mixing and matching, so that health care providers may become skilled in its use and the typical timing when changes in the settings for mechanical ventilation can be anticipated.

In summary, all mothers threatening preterm delivery should be given one to two courses of antenatal corticosteroids according to the National Institute of Health Consensus Statement Guidelines.⁷³ All three available surfactants (i.e., beractant, calfactant and poractant alfa) are clinically efficacious when used for prophylaxis or treatment of established RDS. At present, head-to-head trials comparing the preparations are too small to detect important differences. Trial confounders such as early extubation to nasal CPAP, the use of methylxanthines, and differences in ventilator weaning strategies make interpretation of the literature even more challenging. The use of prophylactic surfactant is advisable in all infants less than or equal to 30 weeks gestation. Repeat doses should be used when clinically indicated.

Chronic lung disease is the consequence of iatrogenically-induced lung damage from prolonged ventilator use in the treatment of RDS. The importance of proper ventilator weaning techniques and the avoidance of overventilation is well known. Overdistention of the lungs promotes inflammatory mediator release and worsens existing damage. Natural surfactants rapidly improve oxygenation and lung compliance. Without proper clinical diligence, overventilation can occur leading to changes in arterial blood pressure and cerebral blood flow along with hypocarbia, which may predispose to IVH and periventricular leukomalacia. Use of a single surfactant appears most important to avoid confusing monitoring and ventilator management issues that may lead to overventilation with its associated risks. Until further research can prove differences, calfactant, poractant, and beractant must be considered therapeutically equivalent products. Using current dosing guidelines, all three surfactants administer the same amount of phospholipid (Table 1). Although calfactant delivers higher percentage component of SP-B and SP-C, the difference has not adequately been proven to affect response.

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