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Efficacy of Surfactant-TA, Calfactant and Poractant Alfa for Preterm Infants with Respiratory Distress Syndrome: A Retrospective Study

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Purpose: To compare the efficacy of the new drug calfactant with the commonly used drugs surfactant-TA and poractant alfa. **Materials and Methods:** A total of 332 preterm infants at 24–31 weeks' gestation with respiratory distress syndrome (RDS) were enrolled and allocated to three groups according to the surfactant instilled; Group 1 (n=146, surfactant-TA), Group 2 (n=96, calfactant), and Group 3 (n=90, poractant alfa). The diagnosis of RDS and the decision to replace the pulmonary surfactant were left to the attending physician and based on patient severity determined by chest radiography and blood gas analysis. Data were collected and reviewed retrospectively using patient medical records. **Results:** Demographic factors including gestational age, birth weight, Apgar score, clinical risk index for babies II score, and maternal status before delivery were not different between the study groups. Instances of surfactant redosing and pulmonary air leaks, as well as duration of mechanical ventilation, were also not different. Rates of patent ductus arteriosus, intraventricular hemorrhage (≥grade III), periventricular leukomalacia, high stage retinopathy of prematurity, necrotizing enterocolitis (≥stage II), and mortality were also similar, as was duration of hospital stay. Cases of pulmonary hemorrhage and moderate to severe bronchopulmonary dysplasia were increased in Group 3. **Conclusion:** Calfactant is equally as effective as surfactant-TA and poractant alfa. This was the first study comparing the efficacy of surfactant-TA, calfactant, and poractant alfa in a large number of preterm infants in Korea. Further randomized prospective studies on these surfactants are needed.

Key Words: Pulmonary surfactants, beractant, poractant alfa, calfactant, respiratory distress syndrome

INTRODUCTION

Exogenous surfactant replacement therapy has been the only effective treatment for preterm infants with respiratory distress syndrome (RDS) since 1990 and has markedly reduced pneumothorax and mortality.[1,2] Preterm infants born before 32 weeks' gestation have structurally immature lungs at the saccular stage of develop-

ment. Therefore, surface area and diffusion distance for gas exchange are not normal in these preterm infants. Furthermore, preterm infants with RDS have insufficient available surfactant pools, as well as immature surfactant composition and function. The combination of structural immaturity and an insufficient surfactant pool for gas exchange in preterm infants results in RDS.[3] Surfactant of the mature lung is composed of surfactant-specific proteins and lipids, such as dipalmitoylphosphatidylcholine, surfactant protein (SP)-A, SP-B, SP-C, and SP-D, phosphatidylglycerol, and plasmalogen. Hydrophobic surfactant proteins, SP-B and SP-C play a significant role in the adsorption and spread of dipalmitoylphosphatidylcholine and in stabilizing alveoli.[4]

The first successful exogenous surfactant administration in newborn infants with RDS was reported by Fujiwara, et al.[1] in 1980, who derived the surfactant from minced bovine lung. After the first report by Fujiwara, et al.,[1] subsequent trials of surfactant replacement have been performed, and several animal-derived natural surfactants were made.[5] Animal-derived surfactants are expensive and production is limited due to animal availability. Also, these surfactants contain foreign proteins that may be potentially immunogenic and infectious.[6] Synthetic surfactants, which are free of animal proteins, may have advantages over animal-derived surfactants due to their lack of immune reactions, proinflammatory mediators causing bronchopulmonary dysplasia (BPD), and animal-borne infectious agents.[6] They are also reproducible and have fewer production limitations than animal-derived surfactants. Nevertheless, a meta-analysis by Soll and Blanco[7] in 2001 showed that protein-free old generation synthetic surfactants, such as colfosceril or pumactant, were associated with increased mortality and a greater risk of pneumothorax when compared to animal-derived surfactants. The inferiority of old generation synthetic surfactants is due to their absence of SP-B and SP-C, resulting in failure to lower surface tension. Thus, these protein-free old generation synthetic surfactants have dropped out of the market and are no longer used.

Three animal-derived surfactant preparations commonly used nationwide in Korea include surfactant-TA (Surfacten®, Mitsubishi-Tokyo Pharma Corporation, Osaka, Japan), calfactant (Infasurf®, ONY Inc., Amherst, NY, USA), and poractant alfa (Curosurf®, Chiesi Farmaceutici SpA, Parma, Italy). In Korea, Surfacten® came into the market in 1990, Curosurf® in 1996, and recently, Infasurf® in 2009. There are no published studies comparing efficacy and mortality in preterm infants treated with these three animal-derived surfactants in Korea. Randomized controlled trials using primary outcomes such as efficacy and mortality require a long period of time to complete along with a large sample size and considerable costs. To overcome these obstacles, we performed a retrospective study to evaluate whether differences could be found in efficacy, complications, and mortality among three pulmonary surfactants.

MATERIALS AND METHODS

Subjects

The protocol of this study was reviewed and approved by the Institutional Review Board of Busan Paik Hospital (13-010). Preterm infants of 24–31 weeks' gestation were enrolled; these subjects had been admitted to the neonatal intensive care units (NICU) of Busan Paik Hospital between January 2009 and December 2012 and diagnosed with RDS requiring pulmonary surfactant replacement therapy. Preterm infants who had a chromosomal abnormality or life-threatening major congenital malformation, such as cardiac anomaly or pulmonary hypoplasia, were excluded. These conditions acted as confounding factors by interfering with respiratory function and survival rate and were thus unsuitable for evaluating the efficacy of surfactants. The infants were allocated to three groups according to the type of surfactant instilled: Group 1, Surfacten®; Group 2, Infasurf®; Group 3, Curosurf®.

Study protocol

Clinical data were collected retrospectively from medical records. Surfactant was administered as rescue therapy until December 2010; thus, the diagnosis of RDS and the decision to replace pulmonary surfactant were left to the attending physician and were based on patient severity determined by chest radiography and blood gas analysis.[8,9] From January 2011, surfactant was administered as prophylactic therapy in infants <30 weeks' gestation in the delivery room or operation room, according to notification No. 2010-135 of the Ministry of Health and Welfare on January 2011. We chose surfactants in alphabetical order (Curosurf®, Infasurf®, and then Surfacten®), and calfactant was used from 2010 in our NICU.

Surfactants were instilled into the trachea via an endotracheal tube using an orogastric tube. According to the prescribing information for each drug, Surfacten® (Mitsubishi-Tokyo Pharma Corporation, Osaka, Japan) was dissolved in

4 mL of normal saline and instilled at 4 mL/kg (120 mg/kg). Curosurf® (Chiesi Farmaceutici SpA, Parma, Italy) was administered at 2.5 mL/kg (200 mg/kg), and Infasurf® (ONY Inc., Amherst, NY, USA) was administered at 3 mL/kg (105 mg/kg).

Infant and maternal demographic factors included gestational age, birth weight, gender, Apgar score, small for gestational age (SGA), clinical risk index for babies (CRIB) II score, antenatal corticosteroids therapy, maternal pregnancy-induced hypertension, gestational diabetes mellitus, and histologically confirmed chorioamnionitis. Outcomes associated with RDS included a need for surfactant redosing, pulmonary air leak, pulmonary hemorrhage, mechanical ventilation (including non-invasive ventilation such as nasal continuous positive airway pressure), invasive ventilation (or intubation), postnatal steroids therapy, and BPD.

Outcomes associated with prematurity included patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), sepsis, duration of hospital stay, and mortality.

The definition of SGA was a birth weight less than the tenth percentile on the Lubchenco growth curve.[10] Pulmonary air leak included pneumothorax, pneumomediastinum, or pulmonary interstitial emphysema. Pulmonary hemorrhage was diagnosed when bright red blood was spouted out of the endotracheal tube with typical chest radiographic findings and rapid deterioration of the patient. BPD was defined as an oxygen dependency at 36 weeks post-menstrual age with oxygen treatment for at least the first 28 days of life; this disorder was categorized by severity. Mild BPD was defined as breathing room air at 36 weeks post-menstrual age or discharge; moderate BPD was defined as a need for <30% O_2 at 36 weeks post-menstrual age or discharge; and severe BPD was defined as a need for >30% O_2 with or without positive pressure ventilation or continuous positive pressure at 36 weeks post-menstrual age or discharge.[11] IVH and PVL were diagnosed by brain ultrasound and limited to high grade (≥grade III) IVH.[12] ROP was limited to cases requiring laser therapy.[13] NEC was defined using the modified Bell staging criteria and was limited to stage II and stage III.[14] Sepsis was diagnosed upon clinical signs of systemic infection with a positive blood culture.[15]

Statistical analysis

For continuous variables with a normal distribution and homogeneous variance, the ANOVA test with Bonferroni correction was performed for comparison of multiple groups. For variables without a normal distribution or without homogeneous variance, such as gestational age, the Kruskal-Wallis test was performed. The chi-squared test was performed for nominal variables. Multivariate analysis with Bonferroni correction was performed to compare statistically significant variables. All data were analyzed using SAS Enterprise Guide 3.0 (SAS Institute, Cary, NC, USA). Data are given as mean±standard deviation, and *p*-values <0.05 were considered significant.

RESULTS

Infant and maternal demographic factors

A total of 332 preterm infants were enrolled and allocated to three groups [Group 1 (Surfacten®): n=146; Group 2 (Infasurf®): n=96; Group 3 (Curosurf®): n=90].

There were no differences in gestational age, birth weight, gender, Apgar score at 1 and 5 minutes, SGA, CRIB II score, antenatal corticosteroids, antenatal antibiotics, antenatal magnesium sulfate therapy, maternal gestational diabetes mellitus, and chorioamnionitis between the groups. Maternal pregnancy-induced hypertension was higher in Group 3 than in Groups 1 and 2 (Table 1).

Gestational age was $28^{+1}\pm2^{+1}$ weeks, $28^{+3}\pm2^{+1}$ weeks, and $28^{+0}\pm2^{+2}$ weeks, and birth weight was 1145±312 g, 1155±384 g, and 1088±372 g in Groups 1, 2, and 3, respectively.

Outcomes associated with RDS

The need for surfactant redosing was not different between the study groups [Group 1: 25 (17%); Group 2: 16 (17%); Group 3: 21 (23%); p=0.412]. Cases of pulmonary air leak [Group 1: 3 (2%); Group 2: 3 (3%); Group 3: 2 (2%); p=0.861], total duration of mechanical ventilation (Group 1: 15±16 days; Group 2: 16±18 days; Group 3: 17±19 days; p=0.785), duration of invasive ventilation (Group 1: 10±12 days; Group 2: 12±14 days; Group 3: 12±13 days; p=0.889), and cases of postnatal steroid therapy were also similar between the study groups. However, instances of pulmonary hemorrhage, moderate to severe BPD [Group 1: 8 (6%); Group 2: 5 (5%); Group 3: 12 (15%); p=0.041], and postnatal diuretic therapy in Group 3 were higher than Groups 1 and 2 (Table 2).

Outcomes associated with prematurity

Rates of PDA and ligation of PDA, high grade IVH (≥grade

Table 1. Infant and Maternal Demographic Factors

	Group 1 (n=146)	Group 2 (n=96)	Group 3 (n=90)	*p* value
Gestational age (weeks^{+days})	$28^{+1}\pm2^{+1}$	$28^{+3}\pm2^{+1}$	$28^{+0}\pm2^{+2}$	0.435
Birth weight (g)	1145±312	1155±384	1088±372	0.072
Gender, male (%)	68 (47)	52 (54)	45 (50)	0.512
Apgar score at 1 min	4.10±1.6	4.4±1.5	4.6±1.6	0.118
Apgar score at 5 min	6.5±1.5	7.0±1.1	6.7±1.2	0.072
SGA (%)	13 (9)	11 (11)	12 (13)	0.481
CRIB II	8.1±3.7	7.8±3.9	8.5±4.0	0.367
Antenatal corticosteroids	108 (74)	69 (72)	74 (82)	0.295
Antenatal antibiotics	53 (36)	38 (40)	31 (34)	0.760
Antenatal magnesium sulfate	68 (47)	55 (57)	47 (52)	0.258
Maternal GDM	10 (7)	6 (6)	2 (2)	0.286
Chorioamnionitis	9 (6)	12 (12)	4 (4)	0.174
Maternal PIH	15 (10)	14 (15)	21 (23)	0.024*

SGA, small for gestational age; CRIB, clinical risk index for babies; GDM, gestational diabetes mellitus; PIH, pregnancy induced hypertension.
*p-values <0.05.

Table 2. Outcomes Associated with RDS

	Group 1 (n=146)	Group 2 (n=96)	Group 3 (n=90)	*p* value
Surfactant redosing	25 (17)	16 (17)	21 (23)	0.412
Pulmonary air leak	3 (2)	3 (3)	2 (2)	0.861
Total duration of mechanical ventilation	15±16	16±18	17±19	0.785
Duration of invasive ventilation	10±12	12±14	12±13	0.889
Postnatal steroid therapy	29 (20)	26 (27)	29 (32)	0.053
Pulmonary hemorrhage	15 (10)	7 (7)	19 (21)	0.010*
Postnatal diuretic therapy	11 (8)	5 (5)	19 (21)	0.001*
BPD (moderate to severe)	8 (6)	5 (5)	12 (15)	0.041*

RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia.
*p-values <0.05.

III), PVL, high stage ROP requiring laser therapy, NEC (≥stage II), and mortality were similar between the study groups, as was duration of hospital stay. Sepsis was higher in Group 3 than in Groups 1 and 2 (Table 3).

DISCUSSION

In this study, we compared the clinical efficacy of calfactant (Infasurf®), which came into the market recently, with the commonly used surfactants in Korea, surfactant-TA (Surfacten®) and poractant alfa (Curosurf®) among preterm infants with RDS.

Surfactant-TA (Surfacten®) is derived from a minced bovine lung extract to which synthetic lipids are added to make it similar to natural lung surfactants. It has smaller amounts of phospholipids, SP-B, and plasmalogen than calfactant.[2] Calfactant (Infasurf®) is a bovine lung lavage preparation that has higher amounts of phospholipids and SP-B than surfactant-TA.[2] Poractant alfa (Curosurf®) is derived from a minced porcine lung extract that contains the highest amount of plasmalogen; some studies reported that it is associated with a decreased risk of BPD.[16]

Ramanathan[17] reported that poractant alfa was associated with decreased mortality rates compared to beractant or calfactant, suggesting that the differences in mortality rates may be related to the composition of surfactants, such as higher amounts of phospholipids and plasmalogens and a smaller volume of poractant alfa than other animal-derived surfactants. A meta-analysis by Singh, et al.[18] showed reduced mortality and redosing rates with poractant alfa at 200 mg/kg compared with beractant. However, the reduction was not significant for poractant alfa at 100 mg/kg compared with beractant. They suggested that the greater amounts of phospholipid, SP-B, and SP-C in 200 mg/kg of poractant alfa may have resulted in better outcome regardless of the source of the surfactants. A retrospective observational cohort study in the US compared poractant alfa with calfactant and beractant.[19] They also concluded that poractant alfa at 200 mg/kg was associated with reduced mortality rates

Table 3. Outcomes Associated with Prematurity

	Group 1 (n=146)	Group 2 (n=96)	Group 3 (n=90)	*p* value
Ligation of PDA	17 (12)	17 (18)	14 (16)	0.411
IVH (≥grade III)	16 (11)	10 (10)	18 (20)	0.094
PVL	3 (2)	3 (3)	6 (7)	0.175
ROP (laser therapy)	20 (16)	13 (14)	14 (17)	0.863
NEC (≥stage II)	4 (3)	2 (2)	3 (3)	0.871
Hospital stay	58±26	65±28	67±33	0.072
Mortality	16 (11)	4 (4)	10 (11)	0.143
Sepsis	16 (11)	14 (15)	26 (29)	0.001*

PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis.
*p-values <0.05.

compared with calfactant at 105 mg/kg or beractant at 100 mg/kg. The same dose of poractant alfa and beractant at 100 mg/kg resulted in no difference in mortality rates, and mortality rates were also similar when comparing calfactant and beractant.

Trembath, et al.[20] conducted a retrospective multicenter study in 2013. A total of 51282 infants admitted to 322 NICUs in the US received surfactant replacement with beractant, calfactant, or poractant alfa. There were no differences in outcomes such as air leak syndromes, BPD, NEC, IVH (grade III or IV), and mortality. The authors concluded that the differences in mortality and outcomes between surfactants, found in a large number of previous studies, do not demonstrate the true differences in the effectiveness of surfactants but are related to the outcome variations attributable to different institutions. The study by Trembath, et al. was a multicenter study with a large cohort of infants; however, it was a retrospective study rather than a randomized prospective study. Additionally, infants less than 37 weeks' gestation were included, the median gestational age was 30 weeks, and the median birth weight was 1435 g. In our study, preterm infants less than 32 weeks' gestation were included and had a mean gestational age of 28^{+1} weeks and a mean birth weight of 1130 g; therefore, they were both less mature and smaller than the infants studied by Trembath, et al. Thus, the results by Trembath, et al. cannot be equally applied to all preterm infants with RDS.

In our study, rates of maternal pregnancy-induced hypertension, pulmonary hemorrhage, and moderate to severe BPD were higher in Group 3, the poractant alfa group. As our study was not a randomized prospective study, the clinical data were collected retrospectively. Therefore, we could not avoid selection bias despite the lack of differences between demographic factors including gestational age, birth weight, Apgar score, CRIB II score, and maternal status before delivery. The CRIB score is a risk-adjustment instrument used widely in the NICU. To minimize the problems of treatment bias of the CRIB score, the CRIB II score was developed as an updated and simplified measurement in relation to mortality and major morbidity.[21] In our study, CRIB II scores were similar between groups (Group 1: 8.1±3.7; Group 2: 7.8±3.9; Group 3: 8.5±4.0; p=0.367). According to the first National Institute of Child Health and Human Development Neonatal Research Network study in the US, most early deaths occurred at 22 and 23 weeks, and the mortality rate and morbidities such as IVH (≥grade III) markedly increased between 22 and 23 weeks [mortality rate: 94% at 22 weeks, 74% at 23 weeks, and 45% at 24 weeks; IVH (≥grade III): 38% at 22 weeks, 36% at 23 weeks, and 26% at 24 weeks].[22] Therefore, we excluded infants at 22 and 23 weeks' gestation and only compared those at ≥24 weeks' gestation among the three study groups. If severe infants were enrolled more in Group 3 than in Groups 1 and 2, this would indicate inevitable selection bias as a shortcoming of this retrospective study, despite adjusting for confounding variables and finding similarities in gestational age, birth weight, Apgar scores, and CRIB II scores between groups. Thus, randomized prospective studies comparing the efficacies of animal-derived surfactants are required.

Protein-free old generation synthetic surfactants are not used due to the absence of SP-B and SP-C, as well as failure to lower surface tension, as previously mentioned in the Introduction. Lucinactant, a next-generation synthetic surfactant containing a protein analog of SP-B in animal-derived surfactants, has been developed; this has been found to reduce RDS, compared with colfosceril or other old generation synthetic surfactants, although there was no difference when compared with beractant.[23] Lucinactant also reduced BPD more than colfosceril and decreased RDS-related mor-

tality more than both colfosceril and beractant. Lucinactant was also found to be more effective than colfosceril in the prevention of RDS in the "Lucinactant Trials."[23] A 1-year follow-up study of the Lucinactant Trials concluded that lucinactant was "just as good, if not superior, to animal-derived surfactants in the prevention of RDS and may be a viable alternative to animal-derived products."[24] Thus far, animal-derived surfactants seem to be better than lucinactant for the treatment of RDS and for the prevention and decrease of complications related to RDS, such as pulmonary air leak, BPD, and mortality. Further comparative prospective studies between animal-derived surfactants and next-generation synthetic surfactants such as lucinactant are required.

RDS causes significant mortality in preterm infants; thus, exogenous surfactant replacement has been the only effective treatment for RDS and has markedly decreased mortality rates of preterm infants with RDS. Therefore, surfactant replacement therapy in RDS is very important, and the most effective surfactant must be chosen. While a large number of studies and meta-analyses comparing the effectiveness of surfactants have been performed, they have yielded conflicting results.

In this study, calfactant (Infasurf®), which entered the market recently in Korea, was found to be equally as effective as surfactant-TA (Surfacten®) and poractant alfa (Curosurf®). Further randomized prospective studies comparing these surfactants are required. This is the first study comparing the efficacy of surfactant-TA, calfactant, and poractant alfa in a large number of preterm infants in Korea.

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Comparative Effectiveness of 3 Surfactant Preparations in Premature Infants

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Objective To compare effectiveness of 3 surfactant preparations (beractant, calfactant, and poractant alfa) in premature infants for preventing 3 outcomes: (1) air leak syndromes; (2) death; and (3) bronchopulmonary dysplasia (BPD) or death (composite outcome).

Study design We conducted a comparative effectiveness study of premature infants admitted to 322 neonatal intensive care units in the US from 2005-2010 who were treated with beractant, calfactant, or poractant alfa. We compared the incidence of air leak syndromes, death, and BPD or death, adjusting for gestational age (GA), antenatal steroids, discharge year, and small for GA status.

Results A total of 51 282 infants received surfactant; 40% received beractant, 30% calfactant, and 30% poractant alfa. Median birth weight was 1435 g (IQR 966-2065); median GA was 30 weeks (27-33). On adjusted analysis, we observed a similar risk of air leak syndromes (calfactant vs beractant OR = 1.17 [95% CI: 0.95, 1.43]; calfactant vs poractant OR = 1.23 [0.98, 1.56]; beractant vs poractant OR = 1.06 [0.87, 1.29]), death (calfactant vs beractant OR = 1.14 [0.93, 1.39]; calfactant vs poractant OR = 0.98 [0.78, 1.23]; beractant vs poractant OR = 0.86 [0.72, 1.04]), and BPD or death (calfactant vs beractant OR = 1.08 [0.93, 1.26]; calfactant vs poractant OR = 1.19 [1.00, 1.41]; beractant vs poractant OR = 1.10 [0.96, 1.27]).

Conclusions Beractant, calfactant, and poractant alfa demonstrated similar effectiveness in prevention of air leak syndromes, death, and BPD or death in premature infants when adjusted for site. Previously described differences in mortality between surfactants likely do not represent true differences in effectiveness but may relate to site variation in outcomes. *(J Pediatr 2013;■:■-■).*

Respiratory distress syndrome (RDS) causes significant morbidity and mortality in premature infants. Exogenous surfactant replacement therapy for the treatment of RDS in premature infants decreases severe RDS, pulmonary air leak syndromes, and death.[1] Three animal-derived surfactants are commercially available in the US—beractant (Survanta; AbbVie Inc, Chicago, Illinois), calfactant (Infasurf; Ony, Inc, Amherst, New York), and poractant alfa (Curosurf; Cornerstone Therapeutics Inc, Cary, North Carolina). All 3 preparations are approved by the Food and Drug Administration for use in infants to treat RDS. Over the last 10 years, the use of surfactant in the US has changed little, from 16%-19% among infants admitted to a neonatal intensive care unit (NICU).[2] However, the relative use of specific surfactant preparations has changed significantly. The use of beractant has decreased from 95%-42% of all surfactant administrations, and the use of calfactant and poractant alpha has increased from 5%-27% and 0%-29%, respectively.[2]

Understanding the comparative effectiveness of surfactant preparations is important for reducing neonatal morbidity and mortality. However, randomized trials comparing the efficacy of surfactant preparations have often demonstrated equivocal results or were terminated early due to lack of enrollment.[3-6] No completed prospective studies directly comparing the efficacy of the 3 surfactants within the same trial exist. Further study through a head-to-head randomized trial of surfactant therapy is unlikely largely because of cost and recruitment issues, thus, retrospective comparative effectiveness analyses or meta-analyses are justified to determine the differences, if any, between surfactant preparations.

A recent retrospective cohort study suggested that poractant alfa was associated with a reduced risk for in-hospital mortality compared with calfactant and beractant

BPD	Bronchopulmonary dysplasia
GA	Gestational age
NICU	Neonatal intensive care unit
RDS	Respiratory distress syndrome

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*A list of members of the Best Pharmaceuticals for Children Act—Pediatric Trials Network is available at www.jpeds.com (Appendix).

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(though comparison with beractant was not statistically significant).[7] Other experts have argued that this conclusion is problematic as it is based on a retrospective study of an administrative data set that is not a part of a daily documentation system.[8] In addition, a significant portion of the sample was not included in final models for analysis. A meta-analysis examining randomized trials of porcine vs bovine surfactants in RDS also suggests that infants treated with poractant alfa have a decreased risk of death compared with those treated with beractant.[9] The trials included in the meta-analysis, which date from 1995-2005, represent a small number of patients and may not be representative of current clinical practice or effectiveness. We compared the effectiveness of beractant, calfactant, and poractant alfa for preventing 3 outcomes: (1) air leak syndromes; (2) death; and (3) bronchopulmonary dysplasia (BPD) or death (composite outcome).

Methods

We conducted a comparative effectiveness study using an administrative database of infants discharged from 322 NICUs managed by the Pediatrix Medical Group from January 1, 2005-December 31, 2010. Clinicians who provide direct care to infants in these NICUs generate data on a daily basis for the purposes of creating progress notes and medical billing. Daily notes are stored in an electronic database along with administered medications and diagnoses. From the daily notes, data are extracted, de-identified (in compliance with the Health Insurance Portability and Accountability Act of 1996) and consolidated into the Pediatrix BabySteps Clinical Data Warehouse. This study was approved by the Duke University Institutional Review Board and Western Institutional Review Board.

We included all inborn infants with a gestational age (GA) <37 completed weeks who were cared for at a single NICU and received beractant, calfactant, or poractant alfa. We excluded infants admitted to NICUs that administered surfactant to <50 infants over the study period, as well as infants who received >1 surfactant preparation (**Figure**).

Air leak syndrome was defined as a diagnosis of pneumothorax or pulmonary interstitial emphysema following the first exposure to surfactant. Infants <32 weeks GA were classified as having BPD if they received supplemental oxygen or respiratory support (nasal canula, continuous positive airway pressure, or mechanical ventilation) continuously from a corrected GA of 36 0/7-36 6/7 weeks (designated as the test period). Infants ≥32 weeks GA at birth were classified as having BPD if they received supplemental oxygen or respiratory support (nasal canula, continuous positive airway pressure, or mechanical ventilation) continuously from a postnatal age of 28-34 days. The receipt of continuous respiratory support or supplemental oxygen was required to more clearly define infants with BPD compared with those with a transient need for oxygen. Infants on room air without any respiratory support during the respective test period were classified as not having BPD. Infants discharged on room air prior to the test period and not receiving respiratory support on the day of discharge were classified as not having BPD. Those who died before the test period were classified as not having BPD. The outcome of BPD was left as missing if the infant was discharged prior to the test period while receiving supplemental oxygen or respiratory support. The composite outcome of BPD or death was defined as the diagnosis of BPD and/or all-cause in-hospital mortality.

Statistical Analyses

We used summary statistics to describe subjects according to the surfactant administered. We compared categorical and continuous variables across the 3 surfactant types using the χ^2 tests of association and nonparametric Kruskal-Wallis tests, respectively. To account for the correlated structure of our data within NICUs, we fit unconditional logistic regression models as well as mixed models with random and fixed effects for NICUs.

We compared outcomes between infants who received beractant, calfactant, or poractant alfa. Using prior knowledge of potential confounders, we included GA, birth weight, small for GA status, antenatal steroid exposure, sex, race, and discharge year. We used a backward elimination method to determine if our a priori covariates should remain in the model and compared models with the full model containing all covariates using likelihood ratio tests with a significance cut point of <0.1. The final variables included in the model were GA, antenatal steroid exposure, small for GA status, and discharge year.

For each outcome, we used the Hausman specification test to evaluate the correlation between a NICU-specific effect and the included covariates. Given that the Hausman test rejected the null hypothesis ($P < .001$) for each outcome modeled, we concluded that there was correlation between unobserved NICU-specific effects and the variables included in our models. As a result, we opted to use conditional fixed effects logistic regression models for our primary analyses. Conditioning on NICU addressed the heterogeneity of baseline risk of outcomes in each NICU and allowed us to best estimate the treatment effect. The results of unconditional logistic regression and random effects models were also included to compare with estimates from prior studies. Effect measure modification was evaluated by including interaction terms with GA and surfactant and by conducting likelihood ratio tests using a significance cut-point of <0.1. No interaction terms were found to be significant. All analyses were conducted using STATA statistical software v. 12 (StataCorp, College Station, Texas), and a P value of <.05 was considered statistically significant.

Results

We identified 51 282 infants with a median birth weight of 1435 g (IQR 966-2065) and a median GA of 30 weeks (27-33) (**Table I**). Overall, 40% of infants (n = 20 383) were treated with beractant, 30% (n = 15 748) with calfactant, and 30% (n = 15 151) with poractant alfa. During this time period, the use of beractant and calfactant decreased and the use of poractant alfa increased.

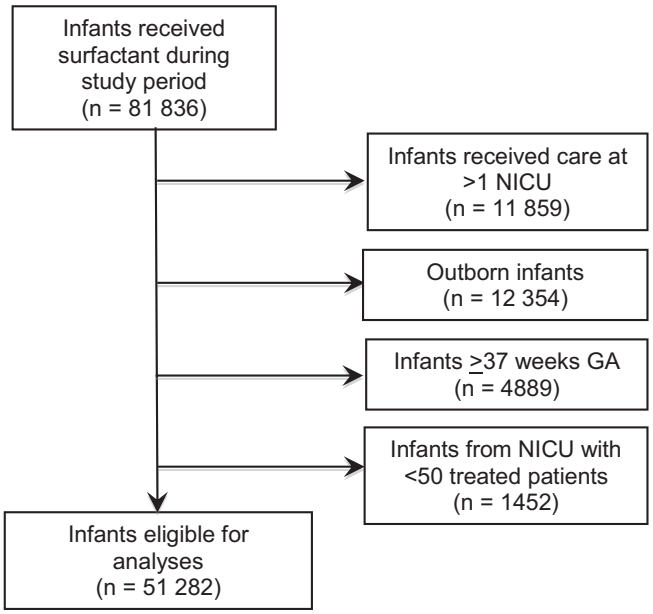

Figure. Flow diagram of study eligibility.

Infants treated with poractant alfa were more mature and larger (median GA 31 weeks [IQR: 28-34], birth weight 1590 g [1050-2220]) compared with those treated with beractant (GA 30 weeks [27-33], birth weight 1390 g [940-2020]) or calfactant (GA 30 weeks [27-33], birth weight 1360 g [930-1960]). A higher proportion of infants treated with calfactant were born to mothers who were treated with antenatal steroids (Table I).

Air leak occurred in 3450 infants (7% overall; 8% beractant, 7% calfactant, 5% poractant alfa). Death occurred in 4576 infants (9% overall; 10% beractant, 9% calfactant, 7% poractant alfa). A total of 12 164 infants (22% overall; 27% beractant, 25% calfactant, 20% poractant alfa) had a diagnosis of BPD or death (composite) (Table II). Three percent of infants (n = 1514) were missing data for determining the outcome of BPD, and 3% (n = 1506) were missing data for the outcome of BPD or death.

Regression Models

Fixed Effects Models. For the outcome of air leak syndromes, we observed no significant differences among the 3 surfactants (calfactant vs beractant OR = 1.17 [95% CI: 0.95, 1.43], calfactant vs poractant OR = 1.23 [0.98, 1.56], and beractant vs poractant OR = 1.06 [0.87, 1.29]) using a fixed effects model (Table III). For the outcome of death alone, the fixed effects model showed no significant differences among the 3 surfactants (calfactant vs beractant OR = 1.14 [0.93, 1.39], calfactant vs poractant OR = 0.98 [0.78, 1.23], beractant vs poractant OR = 0.86 [0.72, 1.04]).

For the combined outcome of BPD or death, the fixed effects model showed no significant differences among the 3 surfactants (calfactant vs beractant OR = 1.08 [0.93, 1.26], calfactant vs poractant OR = 1.19 [1.00, 1.41], and beractant vs poractant OR = 1.10 [0.96, 1.27]).

Simple Logistic Regression and Random Effects Models. For the outcome of air leak syndromes and the composite outcome of BPD or death, there was a statistical difference between poractant vs calfactant or beractant in the simple logistic regression models (air leak syndromes: calfactant vs poractant OR = 1.25 [1.13, 1.40], and beractant vs poractant OR = 1.47 [1.35, 1.61] for BPD or death: calfactant vs poractant OR = 1.04 [0.95, 1.13], and beractant vs

Table I. Patient demographics of treated infants by surfactant preparation, 2005-2010

	Beractant N = 20 383 (%)	Calfactant N = 15 748 (%)	Poractant alfa N = 15 151 (%)	*P*
Admit year				<.001
2005-2007	10 776 (52.8)	8446 (53.6)	5921 (39.1)	
2008-2010	9607 (47.2)	7302 (46.4)	9230 (60.9)	
GA (wk)				<.001
<28	5590 (27.4)	4484 (28.5)	3263 (21.5)	
28-31	10 380 (50.9)	8221 (52.2)	7601 (50.2)	
32-36	4413 (21.7)	3043 (19.3)	4287 (28.3)	
Birth weight (g)				<.001
<500	343 (1.7)	267 (1.7)	219 (1.5)	
500-749	2479 (12.2)	1892 (12.0)	1371 (9.0)	
750-999	2940 (14.4)	2384 (15.1)	1824 (12.0)	
1000-1499	5457 (26.8)	4403 (28.0)	3538 (23.3)	
1500-1999	3917 (19.2)	3068 (19.5)	3204 (21.2)	
≥2000	5243 (25.7)	3731 (23.7)	4995 (33.0)	
Cesarean delivery	14 746 (72.3)	11 436 (72.6)	11 154 (73.6)	.02
Race/ethnicity				<.001
White	9703 (47.6)	8793 (55.8)	9085 (60.0)	
Black	4735 (23.2)	3518 (22.3)	1862 (12.3)	
Hispanic	4562 (22.4)	2316 (14.7)	3086 (20.4)	
Other	814 (4.0)	725 (4.6)	575 (3.8)	
Male sex	11 575 (56.8)	8946 (56.8)	8693 (57.4)	.49
Antenatal steroids	12 889 (63.2)	10 503 (66.7)	9286 (61.3)	<.001
Small for GA	2270 (11.4)	1701 (10.8)	1478 (9.8)	<.001

Table II. Unadjusted patient outcomes during hospitalization by surfactant preparation

Outcome	Beractant	Calfactant	Poractant alfa
Total ventilator days, median (IQR)	2 (1-7)	2 (1-7)	2 (0-5)
Necrotizing enterocolitis (medical and surgical), n (%)	1384 (6.8)	1191 (7.6)	1006 (6.6)
Intraventricular hemorrhage (grade III, IV), n (%)	1008 (5.0)	835 (5.3)	657 (4.3)
Pneumothorax, n (%)	1230 (6.0)	775 (4.9)	616 (4.1)
Pulmonary interstitial emphysema, n (%)	516 (2.5)	356 (2.3)	238 (1.6)
Air leak syndrome, n (%)	1589 (7.8)	1059 (6.7)	802 (5.3)
BPD, n (%)	3475 (17.6)	2480 (16.1)	1889 (12.9)
Death, n (%)	2052 (10.1)	1438 (9.1)	1086 (7.2)
Death or BPD, n (%)	5403 (27.4)	3848 (24.9)	2913 (19.9)

poractant OR = 1.35 [1.26, 1.43]). However, for the outcome of death no difference was noted between calfactant and poractant (calfactant vs poractant OR = 1.04 [0.95, 1.13]). The random effects models showed similar statistical results to the fixed effects models with the exception of air leak syndromes (calfactant vs poractant OR = 1.23 [1.04, 1.44] and beractant vs poractant OR = 1.31 [1.13, 1.51]).

Discussion

In this large cohort of infants, we found that beractant, calfactant, and poractant alfa had similar relative effectiveness at preventing air leak syndromes, death, and BPD or death in premature infants. These results are important as they indicate that there may be no clear advantage of 1 surfactant over another based on important outcome measures. Given our sample size of approximately 15 000 infants treated with poractant and 15 000 infants treated with beractant, we had 80% power to demonstrate a 1.4% absolute difference for the combined outcome of BPD or death.

Air leak syndromes are associated with short- and long-term morbidities including hypotension, hypoxia, and intraventricular hemorrhage. Surfactant administration decreases air leak syndromes such as pneumothorax and pulmonary interstitial emphysema compared with placebo.[5,8-12] In this study, we found 3 surfactant preparations to be similar to each other in preventing air leak syndromes. Overall, the incidence of air leak has decreased significantly in the last several decades, likely because of a number of factors including noninvasive ventilation, improvements in the technology of mechanical ventilation, and surfactant therapy.[13-16] The incidence of pneumothorax among infants <30 weeks GA in this study was similar to the incidence across the Vermont Oxford Network (0%-8.6% from 2005-2010), supporting the assumption that these data are representative of national estimates.[17]

BPD is the most common serious pulmonary outcome in premature infants and is inversely proportional to GA and birth weight.[18] The incidence of BPD has not decreased despite advances in respiratory care, in part because of increased survival of the lowest GA infants who are at highest risk of BPD.[14] Because surfactant therapy decreases the severity of RDS, it was believed that surfactant might also lower the incidence of BPD. In addition, it seemed possible that differences in surfactant preparations, such as surfactant proteins, might affect the incidence of BPD. However, previous studies have not demonstrated a significant difference in the risk of BPD with surfactant use or between different surfactant preparations.[3,4,19] Likewise, we observed no differences in the incidence of BPD or death among surfactant preparations.

Prior to the availability of surfactant, mortality was a common outcome for extremely premature infants.[20] During our study period, mortality decreased among all but the lowest GAs, with infants born at <24 weeks gestation. This is consistent with 2010 data from the Vermont Oxford Network, which showed that mortality among infants with birth weights between 500 and 1500 g was at 65% in those <23 weeks GA.[17]

Surfactant therapy was originally developed to decrease the severity of RDS in extremely and moderately preterm infants. Food and Drug Administration labeling for all 3 surfactants is based on studies that focused on infants <30 weeks GA and birth weights <1250 g or those with evidence of significant

Table III. Comparison of simple logistic regression and random and fixed effects mixed models, OR (95% CI)

	Comparison	Logistic regression	Random effects	Fixed effects
Air leak syndromes	Calfactant vs beractant	0.85 (0.78, 0.92)*	0.94 (0.81, 1.08)	1.17 (0.95, 1.43)
	Calfactant vs poractant	1.25 (1.13, 1.40)*	1.23 (1.04, 1.44)*	1.23 (0.98, 1.56)
	Beractant vs poractant	1.47 (1.35, 1.61)*	1.31 (1.13, 1.51)*	1.06 (0.87, 1.29)
Death	Calfactant vs beractant	0.87 (0.81, 0.94)*	0.99 (0.85, 1.15)	1.14 (0.93, 1.39)
	Calfactant vs poractant	1.04 (0.95, 1.13)	1.05 (0.88, 1.24)	0.98 (0.78, 1.23)
	Beractant vs poractant	1.19 (1.09, 1.29)*	1.06 (0.91, 1.24)	0.86 (0.72, 1.04)
BPD or death	Calfactant vs beractant	0.81 (0.76, 0.85)*	1.01 (0.88, 1.16)	1.08 (0.93, 1.26)
	Calfactant vs poractant	1.10 (1.02, 1.16)*	1.15 (0.98, 1.35)	1.19 (1.00, 1.41)
	Beractant vs poractant	1.35 (1.26, 1.43)*	1.14 (1.00, 1.30)	1.10 (0.96, 1.27)

*$P < .05$.

RDS.[5,19,21] However, nearly one-half of the infants in our cohort were either moderate- (GA between 31 0/7 and 33 6/7 weeks) or late-preterm infants (GA between 34 0/7 and 36 6/7 weeks). Consistent with reports from the few prior studies, our results suggest that a substantial portion of surfactant is used off-label and that current practices are not evidence-based. As the number of preterm deliveries continues to increase, of which late-preterm infants comprise the largest fraction, the role of surfactant in this population needs to be closely evaluated.

The comparative effectiveness of surfactants has become a controversial topic.[8,22-24] In the study by Ramanathan et al, they conclude that "poractant alfa treatment for RDS was associated with a significantly reduced likelihood of death when compared with calfactant and a trend toward reduced mortality when compared with beractant."[7] However, "there were 8276 patients who met the selection criteria, yet were excluded due to unreported, missing, or invalid entries for one or more of the variables: sex, race, All Patient Refined Diagnosis Related Groups, GA or birth weight; the exclusion of these left 14 173 patients for use in the revised regression models."[8] Our results, based on a larger and less selected data sample, do not support the conclusions offered by Ramanathan et al.

Site variation has been clearly linked to unexplained differences in outcomes such as BPD and death in other studies. For example, the risk of BPD ranged from 7%-48% among the Neonatal Research Network centers in a randomized controlled trial of benchmarking to reduce BPD in infants <1250 g birth weight.[25] This variation was not explained by differences in birth weight, GA, race, frequency of prenatal steroid use, or incidence of RDS. Therefore, models that do not adequately account for site variation may produce estimates that are difficult to interpret.

Differences between estimates of effectiveness among surfactant preparations in prior studies and this study may be partially attributable to definitions and statistical methods, including use of different modeling strategies. Modeling, in general, is used to evaluate the association between an outcome of interest, such as death, and a main predictor of interest, such as surfactant preparation, while controlling for other covariates. In simple logistic regression, observations are assumed to be independent from each other. In cases where subjects are clustered by center, this assumption may not be valid. Center-level effects may influence associations between the predictor of interest and outcome.[26] Random or fixed effects models measure change within a group (eg, an individual center) and are often used to account for these center-specific effects. By measuring change within a center across multiple infants, these models can control for a number of potential omitted variables unique to each center. Random effects models assume that center-specific effects are uncorrelated with the other independent variables of the model, and fixed effects do not require this assumption be met. This is an advantage of fixed effects models in certain circumstances, as they remove potential bias that could result from the correlation between site-specific effects and the independent variables. In our study, we believe that certain site-specific effects may have been correlated with the choice of surfactant, making a fixed effects modeling strategy more appropriate. This assumption was supported by the results of the Hausman test. We therefore chose the fixed effects model to provide a more conservative estimate of the true association between surfactant and outcome. The results from this more conservative modeling strategy were significantly different from those using simple logistic regression, which likely overestimated the association between surfactant type and outcomes. Our study is limited by lack of randomization, and we may not have accounted for all known and unknown confounders.

In recent years, the need for comparative effectiveness research has been fueled by the emergence of new pharmaceuticals in the marketplace, as well as a push for cost containment in medication expenditures. However, an important purpose for comparative effectiveness research is also to assist decision-making by clinicians and purchasers to improve the delivery of care.[27] Prior studies have demonstrated the efficacy and cost effectiveness of surfactant as compared with placebo in the setting of randomized controlled trials; however, few have considered the effectiveness of surfactant preparations compared with one another. Surfactant is an effective therapy, and further studies that would compare all 3 surfactant preparations to placebo are unethical. Thus, comparative effectiveness is one of the few methods available to understand how these products are performing in clinical practice.[27]

In summary, we found no significant differences in the outcomes of air leak syndromes, death, and BPD or death between infants treated with beractant, calfactant, and poractant alfa. Also, nearly one-half of infants treated with surfactant were moderate- or late-preterm infants, representing a significant amount of off-label use of this medication. Previously described differences in mortality between surfactants likely do not represent true differences in effectiveness but are accounted for by unmeasured site variation in outcomes. Therefore, the decision regarding which surfactant preparation to use should be based on factors other than effectiveness. ■

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Appendix

Members of the Best Pharmaceuticals for Children Act—Pediatric Trials Network include:

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Comparison of Infasurf (Calf Lung Surfactant Extract) to Survanta (Beractant) in the Treatment and Prevention of Respiratory Distress Syndrome

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ABSTRACT. *Objective.* **To compare the relative safety and efficacy of Infasurf (calf lung surfactant extract; ONY, Inc, Amherst, NY, IND #27169) versus Survanta (Beractant, Ross Laboratories, Columbus, OH) in reducing the acute severity of respiratory distress syndrome (RDS) when given at birth and to infants with established RDS.**

Design. **A prospective, randomized, double-blind, multicenter clinical trial.**

Setting. **Thirteen neonatal intensive care units participated in the treatment arm: seven of these concurrently participated in the prevention arm.**

Patients. **The treatment arm enrolled infants of 2000 g birth weight with established RDS, and the prevention arm enrolled infants of 29 weeks' gestation with birth weights <1250 g.**

Intervention. **Infants were randomly assigned to receive Infasurf (n = 303, treatment arm; n = 180, prevention arm) or Survanta (n = 305, treatment arm; n = 194, prevention arm) in accordance with the Survanta package insert instructions.**

Outcome Measures. **We projected a 25% reduction between groups in the need for a third dose of surfactant for infants with established RDS, and a 25% reduction in the need for a second dose of surfactant for infants who received prophylactic surfactant. Secondary outcomes included the severity of RDS measured by inspired oxygen concentrations and mean airway pressure, air leaks, complications associated with surfactant administration, and survival to 36 weeks' postmenstrual age without the need for oxygen supplementation.**

Results. **In the treatment arm, there was no difference between groups in the number of infants requiring more than two doses of surfactant. The interval between doses was significantly longer for Infasurf, suggesting an increased duration of treatment effect. The inspired oxygen concentration and mean airway pressure were lower in the Infasurf infants during the first 48 hours in the treatment arm.**

In the prevention arm, there were no differences with respect to the number of surfactant doses. The dosing intervals were longer for Infasurf infants after the second dose. No difference in inspired oxygen or mean airway pressure was noted during the first 72 hours.

There were no significant differences in the incidence of air leaks, complications associated with dosing, complications of prematurity, mortality, or survival without chronic lung disease in the prevention or treatment arm.

Conclusions. **Infants treated with Infasurf have a modest benefit in the acute phase of RDS. Infasurf seems to produce a longer duration of effect than Survanta.** *Pediatrics* **1997;100:31–38;** ***respiratory distress syndrome, surfactant, Infasurf, Survanta.***

ABBREVIATIONS. SP-B, surfactant apoprotein B; RDS, respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen; MAP, mean airway pressure.

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Clinical trials with natural surfactant preparations have documented reductions in acute respiratory disease, air leaks, bronchopulmonary dysplasia, and mortality in preterm infants.[1–9] Variations in patient selection criteria, total dose, timing of the initial dose, and dosing schedules preclude a comparison of relative efficacy or safety of these surfactants from previous trials.

Differences in the characteristics of available surfactant preparations have been documented by in vitro biophysical measurements and physiological animal experiments.[10–13] Infasurf and Survanta both use bovine lung as a source. They are similar in that both contain phospholipids, neutral lipids, fatty acids, and hydrophobic surfactant apoproteins, but the proportions of the active ingredients are different.

Survanta has a modified lipid profile as compared with the lung tissue mince extract. Cholesterol is removed and dipalmitoyl-phosphatidylcholine, palmitic acid, and tripalmitin are added, so free fatty acid and neutral lipids are each approximately 10% of total phospholipids (wt/wt).[14] Total protein in Survanta is 1% of the phospholipid (wt/wt) of which 99% is surfactant apoprotein C. Surfactant apoprotein B (SP-B) is present in trace amounts, <.5% of total protein (wt/wt).[15,16]

Infasurf is an extract of the surfactant lavaged from the alveolar spaces and contains the same lipid profile as natural surfactant including cholesterol 5% by weight. It contains minimal free fatty acid, approximately 1% of total phospholipids (wt/wt). Total protein is approximately 2% of total phospholipid (wt/wt) with 40% SP-B and 60% surfactant apoprotein C.[15,16]

In biophysical testing, Infasurf develops lower surface tension than Survanta.[17] In the excised lung model, Infasurf restores total surfactant activity, whereas Survanta restores only a portion of full activity.[10] Mizuno and co-workers[18] improved the activity of Survanta in the premature rabbit by adding large amounts of SP-B (2% by weight) to Survanta. In premature surfactant deficient lambs, Infasurf was more active than Survanta in improving oxygenation and increasing compliance and its activity was sustained longer.[10]

Because of the biochemical and functional differences, we believed a clinical trial to compare these two surfactants was warranted. We conducted this comparison to test for differences in the acute course of RDS which we considered relevant in a comparison of relative surfactant activity.

METHODS

This prospective, randomized, and double-blind clinical trial was divided into a treatment arm (infants of ≤2000 g birth weight with established RDS) and a prevention arm (infants of ≤29 weeks gestation with birth weights <1250 g treated at birth). Both arms were developed to test the effects of the two surfactants in reducing the acute severity of RDS.

The treatment arm was conducted in 13 neonatal centers (participants listed in the Acknowledgments). Seven of the 13 simultaneously participated in the prevention arm. Informed written parental consent was required and protocols were approved by the Institutional Review Boards of all participating institutions. Informed consent was explicit that parents could choose to have their infants treated with an approved surfactant if they did not wish to enroll in the prospective trial.

The design variable for the treatment arm was a 25% reduction in the need for a third dose of surfactant. The design variable for the prevention arm was a 25% reduction in the need for a second dose of surfactant. As a result of the predicted sample size requirements, we could not reasonably have used chronic lung disease or mortality as the primary outcome.

Secondary outcome variables included ventilation and oxygen use during the first 3 days, the frequency of air leaks, complications associated with the dosing process, and survival to 36 weeks' postmenstrual age without the need for oxygen supplementation.

TABLE 1. Population Characteristics (Treatment Arm)*

	Infasurf (n = 303)	Survanta (n = 305)	*P* Value
Birth weight (mean ± SD)	1162 ± 408 g	1166 ± 401 g	.92
Gestational age (mean ± SD)	29.2 ± 2.8 wk	29.2 ± 2.8 wk	.80
Male	57	58	.94
Race, % white	51	48	.47
Singleton births	74	78	.30
Small for gestational age	12	10	.69
Born at study site	66	64	.73
Maternal hypertension	19	16	.29
Maternal temperature >38°C	11	10	.79
Previa or abruption	18	21	.35
Rupture of membranes >24 h	20	20	.92
Mg, Indocin or β agonists	49	46	.63
Vaginal delivery	46	50	.33
Prenatal steroids ≥48 h	12	9	.31
1-Minute Apgar ≤3	27	32	.14
5-Minute Apgar ≤3	5	6	.49

* Unless otherwise noted numbers represent percent.

Enrollment and Randomization

Infants <2000 g birth weight (no minimum) and <48 hours of age, with radiographically confirmed RDS, requiring endotracheal intubation and an F_{IO_2} ≥.4 with a Pa_{O_2} < 80 Torr or an a/A oxygen ratio of ≤.22 were enrolled into the treatment arm.

Mothers who presented in labor or were expected to deliver before 30 weeks gestation (no minimum) were asked to enroll their infants in the prevention arm. Exclusion from enrollment was required if the infant was >1250 g birth weight or >15 minutes old before resuscitation was successful. Outborn infants were excluded from analysis in the prevention arm.

Infants were excluded from either arm if they had a major anomaly which interfered with lung development or function, eg, cyanotic congenital heart disease, diaphragmatic hernias or other causes of pulmonary hypoplasia, hydrops fetalis, or chromosomal anomaly. Exclusion after surfactant treatment occurred if more than one type of surfactant was used during the retreatment process, a dosage error of greater than 50% occurred, a major malformation was recognized after study entry, or congenital sepsis or pneumonia was diagnosed. Exclusions were made without the participant's knowledge of surfactant assignment and randomization codes were not reused after posttreatment exclusions.

Infants were randomly assigned to Survanta or Infasurf by selecting the next vial from a box of sequentially numbered vials. Surfactant was administered within 2 hours of meeting the treatment arm criteria or within 15 minutes of birth in the prevention arm. Stratification into three birth weight groups (≤750, 751 to 1250, and 1251 to 2000 g) was performed in the treatment arm and into two gestational age groups (<27 weeks and 27 to 29 weeks) in the prevention arm. Each center was assigned its own randomization schedule. Variable block size randomization was performed by a pseudo-random number generator and the Moses-Oakford algorithm.

Surfactants

Survanta (Beractant) is a Food and Drug Administration approved drug and is supplied as a 25 mg/mL suspension.[14] Infasurf (calf lung surfactant extract; IND# 27169) has been used in clinical studies at 35 mg/mL concentrations; however, a special 25 mg/mL concentration was used in this trial to maintain masking. The surfactants were therefore of similar consistency, concentration, and color. In addition, the vials were covered by two layers of opaque labels.

Administration, storage, and dispensing of surfactant followed the Survanta package insert. Both surfactants were administered at the recommended dose for Survanta of 100 mg/kg. Three repeat treatments, at least six hours apart, during the first 96 hours were to be given if the infant remained intubated for RDS and in ≥.3 F_{IO_2}. An infant, who received four doses from the assigned surfactant could be crossed over to the other surfactant at the discretion of the attending physician.

Sample Size, Data Collection, and Analysis

It had been shown that 64% of infants with RDS who received Survanta treatment required more than two doses.[19] It was determined that 320 infants with RDS were necessary to detect a 25% difference (α, .05; β, .2) in the treatment arm. Sixty percent of infants who received Survanta prophylaxis had required more

TABLE 2. Respiratory Status (Treatment Arm)*

	Infasurf (n = 303)	Survanta (n = 305)	*P* Value
Study entry status			
Age at entry			
Mean ± SD	7.5 ± 8.1 h	6.4 ± 6.4 h	.08
Median (25th, 75th percentile)	4.7 (3.3, 7.3)	4.3 (2.6, 7.5)	
FIO_2 at entry			
Mean ± SD	74 ± 22 h	76 ± 23 h	.88
Median (25th, 75th percentile)	74 (54, 100)	80 (55, 100)	
Mean airway pressure at entry			
Mean ± SD	8.8 ± 2.9 cm H_2O	9.0 ± 2.8 cm H_2O	.57
Median (25th, 75th percentile)	8 (7, 10)	9 (7, 10)	
$PaCO_2$ at entry			
Mean ± SD	44 ± 12 Torr	43 ± 11 Torr	.25
Median (25th, 75th percentile)	42 (37, 48)	43 (36, 48)	
a/A Pao_2 at entry			
Mean ± SD	0.15 ± 0.06	0.15 ± 0.06	.79
Median (25th, 75th percentile)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	
Change in FIO_2 after 1st dose			
Mean ± SD	−18.3 ± 21.1	−13.0 ± 20.0	.01
Median (25th, 75th percentile)	−22 (0, −48)	−13 (0, −34)	
Change in mean airway pressure after 1st dose			
Mean ± SD	−0.4 ± 1.9 Torr	−0.1 ± 1.9 Torr	
Median (25th, 75th percentile)	0 (0, −10)	0 (0, −6)	
Number of surfactant doses			
Only one dose	30	34	
Only two doses	27	21	
Only three doses	21	12	
Four or more doses	22	33	.002
Dose intervals			
Hours dose 1 to dose 2			
Mean ± SD	13 ± 11 h	10 ± 9 h	<.001
Median (25th, 75th percentile)	8 (7, 15)	7 (6, 8)	
Hours dose 2 to dose 3			
Mean ± SD	13 ± 11 h	9 ± 5 h	<.001
Median (25th, 75th percentile)	8 (7, 17)	7 (6, 10)	
Hours dose 3 to dose 4			
Mean ± SD	12 ± 11 h	8 ± 5 h	.006
Median (25th, 75th percentile)	8 (7, 11)	7 (6, 9)	
Duration of intermittent mechanical ventilation			
Mean ± SD	13 ± 21 d	13 ± 21 d	.99
Median (25th, 75th percentile)	5 (2, 23)	5 (2, 26)	
Duration of supplemental oxygen			
Mean ± SD	29 ± 40 d	30 ± 37 d	.9
Median (25th, 75th percentile)	21 (5, 44)	24 (4, 45)	
Time weighted averages (0 to 72 hours)			
FIO_2	41 ± 16 Torr	44 ± 20 Torr	.03
Mean airway pressure	5.9 ± 2.8 cm H_2O	6.4 ± 3.1 cm H_2O	.04

* Unless otherwise noted numbers represent percent.

than one dose.[19] Therefore, 372 infants were required to detect a 25% difference (α, .05; β, .2) in the prevention arm.

A data coordinator and a neonatologist collected data at each center. Information was recorded for each mother's demographic profile, medical and obstetric history, labor, and delivery. Data from the infant's clinical course were collected daily for the first 45 days, at 36 weeks' postconceptional age, and at discharge to home or death.

Cranial ultrasonography, echocardiograms, and chest radiographs were performed as necessary. Results were interpreted by the cardiologists and radiologists at the participating centers. A diagnosis of patent ductus arteriosus required ultrasound verification. Cranial ultrasounds were classified by the method of Papile.[20] The treatment and occurrence of other complications of prematurity were recorded. Pneumonia was diagnosed when any lung disease was associated with a positive blood culture. As in the Survanta prevention studies, RDS was defined as $FIO_2 > .40$ at any retreatment.[19]

Posthoc analysis of the time-weighted average of FIO_2 and mean airway pressures (MAPs) were done to permit comparison with the National Institutes of Health Exosurf-Survanta study report.[21]

One interim analysis was conducted for each arm by the Data Monitoring and Advisory Committee. The identity of the treatment groups was not revealed to either the committee or the investigators. The number of surfactant doses per patient was lower than expected suggesting that the sample size should be increased. The Data Monitoring Advisory Committee approved an increase in sample size to 600 for the treatment arm. The prevention arm interim analysis indicated a potential difference in mortality. However, the death rate in the low mortality group was much lower than previously reported in other surfactant studies. The enrollment plan of the prevention arm was not modified.

Quantitative variables were compared using analysis of variance and the Mann-Whitney *U* test. For qualitative variables, the Cochran-Mantel-Haenszel χ^2 test was used. The appropriateness of pooling the data from all centers was tested by the Breslow-Day method. All analyses were performed using the Statistical Analysis System (SAS, SAS Institute, Cary, NC).

RESULTS

Treatment Arm

Enrollment started during the spring of 1992 and was completed in August 1993. Six hundred sixty-five infants were enrolled. Three were not randomized. Thirty-seven infants were excluded because of

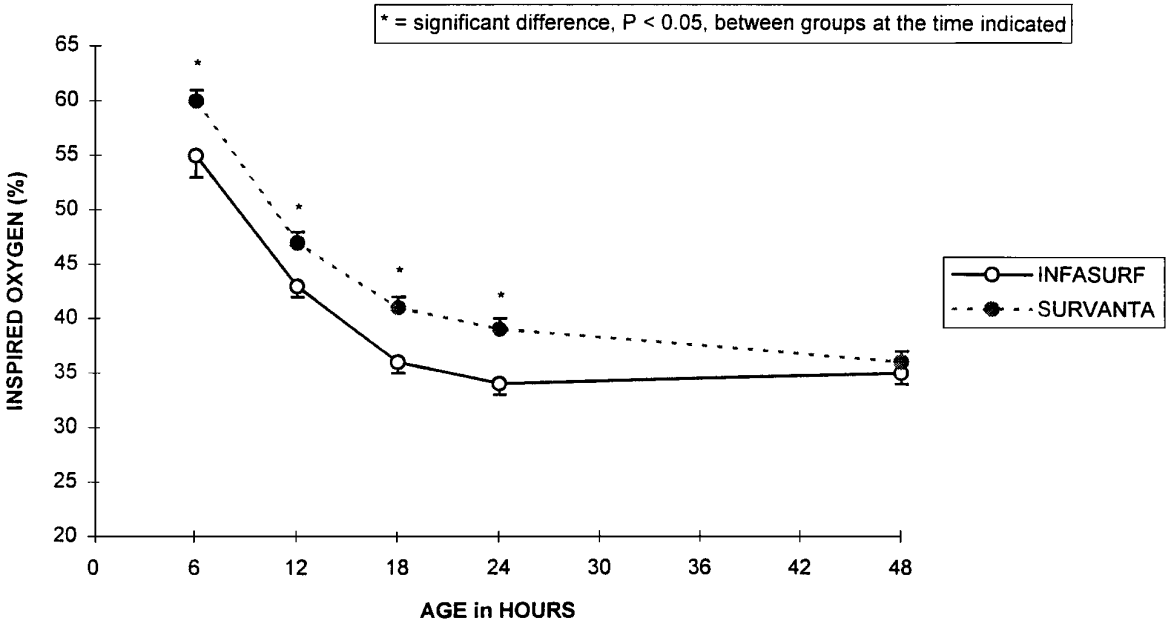

Fig 1. Treatment arm: Inspired oxygen concentration in the Infasurf and the Survanta groups. The mean and standard error is graphed. *Significant difference ($P < .05$) between groups at time indicated.

protocol-defined exclusions and seventeen because of major protocol violations. The primary cause of exclusion for protocol violation was retreatment with the incorrect drug. Center-to-center comparisons of the major outcomes did not reveal any significant difference; therefore, the data from all centers were pooled for analysis. The intent-to-treat analysis results were similar to the evaluable population results that are presented.

The populations were similar in birth weight, gestational age, sex and racial distribution, maternal conditions, prenatal, intrapartum, and delivery room variables including Apgar scores (Table 1).

The age and respiratory status of the two groups were similar at study entry. However, infants receiving Infasurf required significantly less oxygen and had significantly lower MAPs within 1 hour of administration (Table 2). The differences in FIO_2 (Fig 1) and MAP (Fig 2) were sustained throughout the first 24 hours. Time-weighted averages of MAP and FIO_2 were significantly less in the Infasurf group for the first 72 hours (Table 2). There were no differences in the duration of intermittent mechanical ventilation or use of supplemental oxygen throughout the remainder of the hospital stay (Table 2).

The distribution of surfactant dosing is shown in Table 2. Forty-three percent of Infasurf and 45% of Survanta infants received three or more doses ($P = .33$). However, 33% of Survanta-treated infants were given a fourth dose as compared with 22% of Infa-

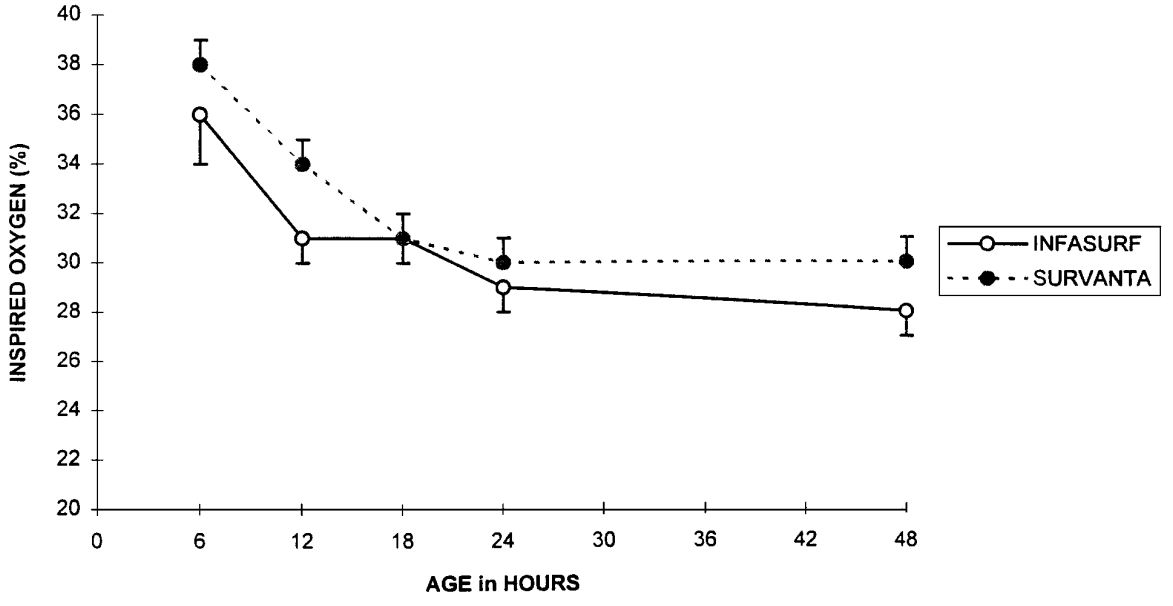

Fig 2. Prevention arm: Inspired oxygen concentration in the Infasurf and the Survanta groups. The mean and standard error is graphed. *Significant difference ($P < .05$) between groups at time indicated.

TABLE 3. Event Reports (Treatment Arm)*

	Infasurf (n = 303)	Survanta (n = 305)	*P* Value
Dosing complications			
Bradycardia during any dose	16	14	.50
Airway obstruction during any dose	2	1	.11
Extubated during any dose	1	0	.12
δ blood pressure ± 5 mm Hg during any dose	16	14	.57
Any dosing complication during any dose	29	26	
Pneumothorax	6	10	.07
Pulmonary interstitial emphysema	10	14	.13
Any air leak	15	18	.27
Pulmonary hemorrhage	6	6	1.00
Patent ductus arteriosus evaluated for patent ductus arteriosus	114/168	118/157	.18
Necrotizing enterocolitis	11	15	.15
Apnea	71	68	.25
Retinopathy of prematurity	17	14	.37
Sepsis	23	24	.85
Number with neuroimaging	275	268	
Grades I and II	30	35	.20
Grades III and IV	11	10	.68
Alive at discharge	82	83	.83
Respiratory distress syndrome deaths	13	13	.9
Alive at 36 wk, no oxygen	63	59	.3

* Unless otherwise noted, numbers represent percent.

surf-treated infants ($P = .002$). The duration of treatment effect was longer for Infasurf infants as measured by the longer dosing interval (Table 2).

No significant differences were noted in the incidence of mortality, chronic lung disease, dosing-related events, or complications of prematurity (Table 3).

Prevention Arm

Enrollment started during the spring of 1992 and was completed in January 1994. Four hundred sixty-three infants were recruited for the study. Six infants were not randomized. Sixty were excluded because of protocol defined exclusions and 23 because of major protocol deviations. Center-to-center comparisons of the major outcomes did not reveal any significance difference; therefore, the data from all centers were pooled for analysis. The intent-to-treat analysis results were similar to the evaluable population results which are presented.

The mean gestational age of the 181 Infasurf and 195 Survanta infants who successfully completed the study was similar, although the mean birth weight of Infasurf infants was greater. No significant differences were noted in gender, race, the number of singletons, or small-for-date infants. Comparison of maternal conditions, prenatal, intrapartum, and delivery room information did not show significant differences (Table 4).

RDS occurred in 43% of Infasurf and 44% of the Survanta infants ($P = .92$). Infasurf infants had significantly longer interdose intervals after dose two, but there was no difference in the number of infants who required the full treatment course (Table 5).

Survival to discharge occurred in 86% of the Infasurf and 92% of the Survanta infants ($P = .06$). However, mortality <600 g birth weight was extremely low in the Survanta group (6 out of 23, 26%) compared with the Infasurf group (19 out of 30, 63%) ($P = .007$).

Supplemental oxygen and MAP were similar throughout the first 72 hours. Survanta infants required more days of intermittent mechanical ventilation and oxygen supplementation (Table 5), primarily because of the survival of those <600 g at birth. There were no significant differences in the incidence of adverse events, survival to 36 weeks' postmenstrual age without the need for oxygen supplementation, or dosing complications (Table 6).

DISCUSSION

Three clinical surfactant comparison studies have been reported. The Vermont-Oxford and National Institutes of Health networks tested Exosurf Neona-

TABLE 4. Population Characteristics (Prevention Arm)*

	Infasurf (n = 180)	Survanta (n = 194)	*P* Value
Birth weight (mean ± SD)	891 ± 221 g	845 ± 205 g	.04
Gestational age (mean ± SD)	27.1 ± 2.2 wk	27.1 ± 2.1 wk	.5
Male	53	46	.18
Race, % white	46	40	.35
Singleton births	79	85	.18
Small for gestational age	12	10	.74
Maternal hypertension	14	16	.57
Maternal temperature >38°C	17	13	.30
Previa or abruption	22	26	.40
Rupture of membranes >24 h	26	30	.38
Mg, Indocin or β agonists	67	63	.39
Vaginal delivery	45	48	.54
Prenatal steroids ≥48 h	28	26	.82
1-Minute Apgar ≤3	30	29	.7
5-Minute Apgar ≤3	4	3	.7

* Unless otherwise noted, numbers represent percent.

TABLE 5. Respiratory Status (Prevention Arm)*

	Infasurf (n = 180)	Survanta (n = 194)	*P* Value
Surfactant doses			
Only one dose	52	51	
Only two doses	16	13	
Only three doses	13	10	
Four or more doses	19	26	.30
Dose intervals (mean ± SD)			
Dose 1 to dose 2			
Mean ± SD	15 ± 12 h	12 ± 12 h	.10
Median (25th, 75th percentile)	9 (7, 19)	8 (7, 12)	
Dose 2 to dose 3			
Mean ± SD	18 ± 19 h	11 ± 8 h	.005
Median (25th, 75th percentile)	9 (7, 20)	8 (7, 11)	
Dose 3 to dose 4			
Mean ± SD	17 ± 16 h	11 ± 8 h	.04
Median (25th, 75th percentile)	8 (7, 22)	8 (7, 14)	
Duration of intermittent mechanical ventilation			
Mean ± SD	20 ± 22 d	27 ± 26 d	.012
Median (25th, 75th percentile)	25 (2, 38)	29 (3, 45)	
Duration of supplemental oxygen			
Mean ± SD	36 ± 39 d	46 ± 48 d	.02
Median (25th, 75th percentile)	40 (16, 45)	43 25, 45)	
Time weighted averages (0 to 72 h)			
FIO_2	32 ± 14 Torr	32 ± 11 Torr	.90
Mean airway pressure	5.8 ± 2.8 cm H_2O	5.5 ± 2.3 cm H_2O	.26

* Unless otherwise noted, numbers represent percent.

TABLE 6. Event Reports (Prevention Arm)*

	Infasurf (n = 180)	Survanta (n = 194)	*P* Value
Dosing complications			
Bradycardia during any dose	14	14	.88
Airway obstruction during any dose	4	2	.13
Extubated during any dose	2	2	1.00
δ blood pressure ± 5 mm Hg during any dose	1	1	.36
Any dosing complication during any dose	18	18	1.00
Any air leak	13	10	.41
Pulmonary hemorrhage	6	6	1.00
Patent ductus arteriosus/evaluated for patent ductus arteriosus	94/120	107/138	1.00
Necrotizing enterocolitis	26	24	.72
Apnea	87	89	.53
Retinopathy of prematurity	27	29	.42
Sepsis	33	32	.91
Number with neuroimaging	175	193	
Grades I and II	37	31	.13
Grades III and IV	5	5	.82
Alive at discharge	86	92	.06
Birth weight <600 g–alive at discharge	37	74	.007
Respiratory distress syndrome deaths	7	2	.01
Alive at 36 wk, no oxygen	67	69	.66

* Unless otherwise noted, numbers represent percent.

tal versus Survanta[21,22] and Hudak and colleagues[23] tested Infasurf versus Exosurf. Each concluded that treatment with natural surfactant, as compared with a synthetic, resulted in a greater reduction in the severity of RDS, two comparisons documented a difference in air leaks, but survival without chronic lung disease was not significantly altered. In this study which compared the two natural (bovine) surfactants, similar differences between surfactants were observed in the treatment arm but not in the prophylaxis arm.

The treatment arm showed that Infasurf, when administered according to the Survanta protocol, produced a greater initial improvement in respiratory status that was better sustained at every dose as evidenced by lower oxygen and MAP and by longer intervals between doses. In addition, there were fewer patients who required the full Infasurf treatment course. Only the longer duration between doses could be replicated in the prevention arm.

In the prevention arm, Survanta-treated infants had longer duration of mechanical ventilation and oxygen supplementation most likely as a result of an unprecedented survival rate in those of <600 g birth weight. The survival rate of this subset of Survanta infants (13 out of 19, 74%) is probably not reproducible because all other published data report that a majority of infants <600 g die whether treated with

TABLE 7. Association of Time-Weighted Percent Oxygen and Mean Airway Pressure to Intact Cardiopulmonary Survival

	Infasurf	Survanta
% FIO_2 0 to 72 hours		
Survived	37 ± 12	36 ± 11
Died or oxygen at 36 weeks	51 ± 21	56 ± 24
P value	<.001	<.001
Mean airway pressure		
Survived	5.3 ± 2.2	5.1 ± 2.3
Died or oxygen at 36 weeks	8.3 ± 3.5	7.8 ± 3.0
P value	<.001	<.001

surfactant or not.[24] Beyond this subgroup's unexplained difference in mortality, safety outcomes, adverse events at administration, and serious complications of prematurity, including chronic lung disease, occurred at similar rates in both treatment groups in both arms of the study.

Early administration of any surfactant to preterm infants at high risk of RDS is more effective than waiting until development of severe respiratory symptoms, as evidenced by lower severity of acute disease and lower incidence of death and chronic lung disease.[25,26] Although this study did not compare prophylaxis to treatment, we note that the duration of effect, for both surfactants, was substantially longer in the prevention arm as compared with the treatment arm.

There are three major compositional differences between Infasurf and Survanta, two of which we speculate account for the biophysical activity and clinical differences. Survanta contains phospholipids from lung cells as well as lung surfactant, it has higher levels of nonphosphatidylcholine phospholipids such as sphingomyelins and phosphatidylethanolamines, and these phospholipids limit the lowest surface tension attainable in bovine surfactant preparations.[27] There is a step in the Survanta process that removes cholesterol which probably also removes the surfactant apoprotein B, the apoprotein most critical for full biophysical activity.[28] Mizuno and associates[18] have shown the levels of SP-B in Survanta to be subthreshold for biologic effect and Survanta activity is improved by supplementing it with SP-B.

The differences between surfactants in biophysical testing and animal models with virtual surfactant depletion are difficult to document in a clinical trial in which almost all patients have endogenous surfactant. It has been proposed that all surfactant drugs, in addition to their independent surfactant activity, interact with existing endogenous surfactant and may serve as substrate for improved endogenous production.[29] The effect in a clinical trial of any surfactant is a combination of surfactant activity, its interaction with endogenous surfactant, and the time at which adequate endogenous material begins to be secreted from the Type II cells. In addition, it is likely that this diminished difference is a reflection of the larger number of confounding variables introduced by the clinical practice arena.

Trials such as this one and others that have compared surfactants, which have treatment groups in the hundreds, not thousands, have only demonstrated the differences in activity of surfactants during the acute phase of RDS. They have not been able to document differences in ultimate outcome. The failure to detect differences in chronic lung disease or mortality could come from inadequate sample size or the lack of effect. Insight can be gained by examining the relationship of the time-weighted averages with ultimate outcome (Table 7). Infants who die or develop chronic lung disease had significantly more severe RDS, in both treatment groups. Based upon this association we speculate that all of these comparison studies would have revealed differences in chronic lung disease and death if they had enrolled enough patients.

This study detected differences in the time interval between doses in a protocol that followed the Survanta package insert guidelines for redosing. Many clinicians are choosing to wait longer, or for more severe lung disease to reappear before retreating than recommended in the Survanta package insert. It is unclear how this practice influences the interpretation of our findings. We are currently conducting a follow-up clinical comparison trial to examine optimum redosing strategies.

SUMMARY

In conclusion there was a modest improvement in the acute phase of respiratory distress measured by MAP, FIO_2, and duration of effect in infants receiving Infasurf in the treatment group. Only the longer duration of effect of Infasurf seems is replicated in the prevention arm. Survival to 36 weeks' postmenstrual age without the need for supplemental oxygen was similar for both surfactants. Both surfactants are associated with marked improvement in severity of RDS and Infasurf seems to have a longer sustained effect.

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TECHNOLOGICAL DISASTER

In football, the rise of the plastic helmet in place of leather, around 1950, allowed the sport to become more brutal, more than tripling the number of neck injuries and doubling the deaths from cervical spine injuries.

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Submitted by Student

Comparison of Infasurf (Calf Lung Surfactant Extract) to Survanta (Beractant) in the Treatment and Prevention of Respiratory Distress Syndrome

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INFASURF ® (calfactant)
Intratracheal Suspension
Sterile Suspension for Intratracheal Use Only

Rx Only Rev. 03/18

DESCRIPTION

Infasurf® (calfactant) Intratracheal Suspension is a sterile, non-pyrogenic lung surfactant intended for intratracheal instillation only. It is an extract of natural surfactant from calf lungs which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C). It contains no preservatives.

Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 - 6.2 (target pH 5.7). Each milliliter of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.7 mg proteins including 0.26 mg of SP-B.

CLINICAL PHARMACOLOGY

Endogenous lung surfactant is essential for effective ventilation because it modifies alveolar surface tension thereby stabilizing the alveoli. Lung surfactant deficiency is the cause of Respiratory Distress Syndrome (RDS) in premature infants. Infasurf restores surface activity to the lungs of these infants.

Activity: Infasurf adsorbs rapidly to the surface of the air:liquid interface and modifies surface tension similarly to natural lung surfactant. A minimum surface tension of ≤3 mN/m is produced in vitro by Infasurf as measured on a pulsating bubble surfactometer. Ex vivo, Infasurf restores the pressure volume mechanics and compliance of surfactant-deficient rat lungs. In vivo, Infasurf improves lung compliance, respiratory gas exchange, and survival in preterm lambs with profound surfactant deficiency.

Animal Metabolism: Infasurf is administered directly to the lung lumen surface, its site of action. No human studies of absorption, biotransformation, or excretion of Infasurf have been performed. The administration of Infasurf with radiolabeled phospholipids into the lungs of adult rabbits results in the persistence of 50% of radioactivity in the lung alveolar lining and 25% of radioactivity in the lung tissue 24 hours later. Less than 5% of the radioactivity is found in other organs. In premature lambs with lethal surfactant deficiency, less than 30% of instilled Infasurf is present in the lung lining after 24 hours.

Clinical Studies: The efficacy of Infasurf was demonstrated in two multiple-dose controlled clinical trials involving approximately 2,000 infants treated with Infasurf (approximately 100 mg phospholipid/kg) or Exosurf Neonatal®. In addition, two controlled trials of Infasurf versus Survanta®, and four uncontrolled trials were conducted that involved approximately 15,500 patients treated with Infasurf.

Infasurf versus Exosurf Neonatal®

Treatment Trial

A total of 1,126 infants ≤72 hours of age with RDS who required endotracheal intubation and had an a/A PO_2 < 0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). Patients were given an initial dose and one repeat dose 12 hours later if intubation was still required. The dose was instilled in two aliquots through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated at 28 days or to discharge for all treated patients from this treatment trial are shown in Table 1.

Table 1- Infasurf vs Exosurf Neonatal®
Treatment Trial

Efficacy Parameter	Infasurf (N=570) %	Exosurf Neonatal® (N=556) %	p-Value
Incidence of air leaks [a]	11	22	≤0.001
Death due to RDS	4	4	0.95
Any death to 28 days	8	10	0.21
Any death before discharge	9	12	0.07
BPD [b]	5	6	0.41
Crossover to other surfactant [c]	4	4	1

[a] Pneumothorax and/or pulmonary interstitial emphysema.
[b] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[c] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 96 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10

Prophylaxis Trial

A total of 853 infants <29 weeks gestation were enrolled into a multiple-dose, randomized, double-blind prophylaxis trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). The initial dose was administered within 30 minutes of birth. Repeat doses were administered at 12 and 24 hours if the patient remained intubated. Each dose was administered divided in 2 equal aliquots, and given through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated to day 28 or to discharge for all treated patients from this prophylaxis trial are shown in Table 2.

Table 2- Infasurf vs Exosurf Neonatal®
Prophylaxis Trial

Efficacy Parameter	Infasurf (N=431) %	Exosurf Neonatal® (N=422) %	p-Value
Incidence of RDS	15	47	≤0.001
Incidence of air leaks [a]	10	15	0.01
Death due to RDS	2	5	≤0.01
Any death to 28 days	12	16	0.10
Any death before discharge	18	19	0.56
BPD [b]	16	17	0.60
Crossover to other surfactant [c]	0.2	3	<0.001

[a] Pneumothorax and/or pulmonary interstitial emphysema.
[b] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[c] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 72 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10

Infasurf versus Survanta®

Treatment Trial

A total of 662 infants with RDS who required endotracheal intubation and had an a/A PO_2 <0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). Repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Results for the major efficacy parameters evaluated at 28 days or to discharge (incidence of air leaks, death due to respiratory causes or to any cause, BPD, or treatment failure) for all treated patients from this treatment trial were not significantly different between Infasurf and Survanta®.

Prophylaxis Trial

A total of 457 infants ≤30 weeks gestation and <1251 grams birth weight were enrolled into a multiple-dose, randomized, double-blind trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). The initial dose was administered within 15 minutes of birth and repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral). Results for efficacy endpoints evaluated at 28 days or to discharge for all treated patients from this prophylaxis trial showed an increase in mortality from any cause at 28 days (p=0.03) and in death due to respiratory causes (p=0.005) in Infasurf-treated infants. For evaluable patients (patients who met the protocol-defined entry criteria), mortality from any cause and mortality due to respiratory causes were also higher in the Infasurf group (p = 0.07 and 0.03, respectively). However, these observations have not been replicated in other adequate and well-controlled trials and their relevance to the intended population is unknown. All other efficacy outcomes (incidence of RDS, air leaks, BPD, and treatment failure) were not significantly different between Infasurf and Survanta® when analyzed for all treated patients and for evaluable patients.

Acute Clinical Effects: As with other surfactants, marked improvements in oxygenation and lung compliance may occur shortly after the administration of Infasurf. All controlled clinical trials with Infasurf demonstrated significant improvements in fraction of inspired oxygen (F_iO_2) and mean airway pressure (MAP) during the first 24 to 48 hours following initiation of Infasurf therapy.

INDICATIONS AND USAGE

Infasurf is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment ("rescue") of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.

Prophylaxis

Prophylaxis therapy at birth with Infasurf is indicated for premature infants <29 weeks of gestational age at significant risk for RDS. Infasurf prophylaxis should be administered as soon as possible, preferably within 30 minutes after birth.

Treatment

Infasurf therapy is indicated for infants ≤72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

WARNINGS

Infasurf is intended for intratracheal use only.

THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING INFASURF, OFTEN RAPIDLY IMPROVES OXYGENATION AND LUNG COMPLIANCE. Following administration of Infasurf, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.

Infasurf therapy is not a substitute for neonatal intensive care. Optimal care of premature infants at risk for RDS and new born infants with RDS who need endotracheal intubation requires an acute care unit organized, staffed, equipped, and experienced with intubation, ventilator management, and general care of these patients.

TRANSIENT EPISODES OF REFLUX OF INFASURF INTO THE ENDOTRACHEAL TUBE, CYANOSIS, BRADYCARDIA, OR AIRWAY OBSTRUCTION HAVE OCCURRED DURING THE DOSING PROCEDURES. These events require stopping Infasurf administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing can proceed with appropriate monitoring.

PRECAUTIONS

When repeat dosing was given at fixed 12-hour intervals in the Infasurf vs. Exosurf Neonatal® trials, transient episodes of cyanosis, bradycardia, reflux of surfactant into the endotracheal tube, and airway obstruction were observed more frequently among infants in the Infasurf-treated group.

An increased proportion of patients with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was observed in Infasurf-treated infants in the Infasurf-Exosurf Neonatal® controlled trials. These observations were not associated with increased mortality.

No data are available on the use of Infasurf in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation.

Data from controlled trials on the efficacy of Infasurf are limited to doses of approximately 100 mg phospholipid/kg body weight and up to a total of 4 doses.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis studies and animal reproduction studies have not been performed with Infasurf. A single mutagenicity study (Ames assay) was negative.

ADVERSE REACTIONS

The most common adverse reactions associated with Infasurf dosing procedures in the controlled trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). These events were generally transient and not associated with serious complications or death.

The incidence of common complications of prematurity and RDS in the four controlled Infasurf trials are presented in Table 3. Prophylaxis and treatment study results for each surfactant are combined.

Table 3 - Common Complications of Prematurity and RDS in Controlled Trials

Complication	Infasurf (N=1001) %	Exosurf Neonatal® (N=978) %	Infasurf (N=553) %	Survanta® (N=566) %
Apnea	61	61	76	76
Patent ductus arteriosus	47	48	45	48
Intracranial hemorrhage	29	31	36	36
Severe intracranial hemorrhage[a]	12	10	9	7
IVH and PVL [b]	7	3	5	5
Sepsis	20	22	28	27
Pulmonary air leaks	12	22	15	15
Pulmonary interstitial emphysema	7	17	10	10
Pulmonary hemorrhage	7	7	7	6
Necrotizing enterocolitis	5	5	17	18

[a] Grade III and IV by the method of Papile.
[b] Patients with both intraventricular hemorrhage and periventricular leukomalacia.

Follow-up Evaluations

Two-year follow-up data of neurodevelopmental outcomes in 415 infants enrolled in 5 centers that participated in the Infasurf vs. Exosurf Neonatal® controlled trials demonstrated significant developmental delays in equal percentages of Infasurf and Exosurf Neonatal® patients.

OVERDOSAGE

There have been no reports of overdosage with Infasurf. While there are no known adverse effects of excess lung surfactant, overdosage would result in overloading the lungs with an isotonic solution. Ventilation should be supported until clearance of the liquid is accomplished.

DOSAGE AND ADMINISTRATION

FOR INTRATRACHEAL ADMINISTRATION ONLY

Infasurf should be administered under the supervision of clinicians experienced in the acute care of newborn infants with respiratory failure who require intubation. Rapid and substantial increases in blood oxygenation and improved lung compliance often follow Infasurf instillation. Close clinical monitoring and surveillance following administration may be needed to adjust oxygen therapy and ventilator pressures appropriately.

Dosage

Each dose of Infasurf is 3 mL/kg body weight at birth. Infasurf has been administered every 12 hours for a total of up to 3 doses.

Directions for Use

Infasurf is a suspension which settles during storage. Gentle swirling or agitation of the vial is often necessary for redispersion. DO NOT SHAKE. Visible flecks in the suspension and foaming at the surface are normal for Infasurf. Infasurf should be stored at refrigerated temperature 2° to 8°C (36° to 46°F). THE 3mL VIAL MUST BE STORED UPRIGHT. Date and time need to be recorded on the carton when Infasurf is removed from the refrigerator. Warming of Infasurf before administration is not necessary.

Unopened, unused vials of Infasurf that have warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Infasurf should not be removed from the refrigerator for more than 24 hours. **Infasurf should not be returned to the refrigerator more than once.** Repeated warming to room temperature should be avoided. Each single-use vial should be entered only once and the vial with any unused material should be discarded after the initial entry.

INFASURF DOES NOT REQUIRE RECONSTITUTION. DO NOT DILUTE OR SONICATE.

Dosing Procedures

General

Infasurf should only be administered intratracheally through an endotracheal tube. The dose of Infasurf is 3 mL/kg birth weight. The dose is drawn into a syringe from the single-use vial using a 20-gauge or larger needle with care taken to avoid excessive foaming. Administration is made by instillation of the Infasurf suspension into the endotracheal tube.

Administration for Treatment of RDS

When used to treat RDS, Infasurf may be administered using either of the following 2 methods:

Exosurf Active Control Trials: Initial and Repeat Dosing

In the Infasurf vs. Exosurf® trials, Infasurf was administered intratracheally through a side-port adapter into the endotracheal tube. Two attendants, one to instill the Infasurf, the other to monitor the patient and assist in positioning, facilitated the dosing. The dose (3 mL/kg) was administered in two aliquots of 1.5 mL/kg each. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Administration was made while ventilation was continued over 20-30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning separated the two aliquots. Repeat doses of 3 mL/kg of birth weight, up to a total of 3 doses 12 hours apart, were given if the patient was still intubated.

Survanta Active Control Trials: Initial and Repeat Dosing

In the Infasurf vs. Survanta® trials, Infasurf was administered through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a $P_aO_2 \leq 80$ torr.

Administration for Prophylaxis of RDS at Birth

Dosing procedures are described under Administration for Treatment of RDS. The amount of a prophylaxis dose of Infasurf should be based on the infant's birth weight. Administration of Infasurf for prophylaxis should be given as soon as possible after birth. Usually the immediate care and stabilization of the premature infant born with hypoxemia and/or bradycardia should precede Infasurf prophylaxis.

Dosing Precautions

During administration of Infasurf liquid suspension into the airway, infants often experience bradycardia, reflux of Infasurf into the endotracheal tube, airway obstruction, cyanosis, dislodgement of the endotracheal tube, or hypoventilation. If any of these events occur, the administration should be interrupted and the infant's condition should be stabilized using appropriate interventions before the administration of Infasurf is resumed. Endotracheal suctioning or reintubation is sometimes needed when there are signs of airway obstruction during the administration of the surfactant.

HOW SUPPLIED

Infasurf (calfactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered glass vials containing 3 mL (NDC 61938-456-03) and 6 mL (NDC 61938-456-06) off-white suspension.

Store Infasurf (calfactant) Intratracheal Suspension at refrigerated temperature 2° to 8°C (36° to 46°F) and protect from light. **THE 3 mL VIAL MUST BE STORED UPRIGHT.** Vials are for single use only. After opening, discard unused drug.

Rx only

Manufactured by:
ONY Biotech Inc.
Amherst, NY 14228

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Surfactant Properties

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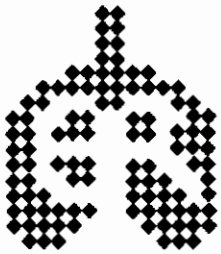

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Surfactant inhibition by plasma proteins: differential sensitivity of various surfactant preparations

W. Seeger, C. Grube*, A. Günther, R. Schmidt

Surfactant inhibition by plasma proteins: differential sensitivity of various surfactant preparations. W. Seeger, C. Grube, A. Günther, R. Schmidt. ©ERS Journals Ltd 1993.
ABSTRACT: Leakage of plasma proteins into the alveolar space may inhibit surfactant function. We compared the surface properties and the sensitivity to inhibitory proteins of different organic solvent surfactant extracts and a synthetic surfactant.

Experiments were performed in the pulsating bubble surfactometer, with surfactant concentrations ranging between 0.1 and 2 mg·ml^{-1}. Inhibition profiles towards fibrinogen, albumin and haemoglobin were obtained from calf lung surfactant extracts (CLSE), Alveofact, Curosurf and Survanta (all used in clinical replacement studies in respiratory distress syndrome (RDS) and of an apoprotein-based synthetic phospholipid mixture (PLM-C/B; DPPC:PG:PA=68.5:22.5:9, supplemented with 2% wt/wt non-palmitoylated human recombinant SP-C and 1% t/wt natural bovine SP-B).

In the absence of inhibitory proteins, all surfactants exhibited dose-dependent rapid adsorption (rank order of relative efficacy PLM-C/B = CLSE > Alveofact > Curosurf > Survanta). Minimal surface tension was reduced to near zero values under dynamic compression (rank order PLM-C/B > CLSE > Alveofact = Curosurf) and to ≈4 mN·m^{-1} (Survanta). Curosurf and Survanta were dose-dependently inhibited by fibrinogen > haemoglobin > albumin, with far-reaching loss of surface activity at protein-surfactant ratios above 1:1. In contrast, CLSE and Alveofact were only moderately inhibited by fibrinogen, and were not affected by haemoglobin and albumin, up to protein-surfactant ratios of 2:1. PLM-C/B exhibited resistance to fibrinogen, intermediate sensitivity to albumin, and was severely inhibited by haemoglobin.

We conclude that various natural surfactant extracts and an apoprotein-based synthetic surfactant mixture markedly differ in their sensitivity to inhibitory plasma proteins. Differences in phospholipid profiles and hydrophobic apoprotein contents (*e.g.* low SP-B quantities in Curosurf and Survanta, high quantities in CLSE and Alveofact) may underlie these findings. Such differences may be relevant for surfactant function under conditions of increased alveolar protein load.
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Surfactant deficiency has been disclosed as the underlying event of the respiratory distress syndrome in preterm infants (RDS) [1–3]. In addition to the primary lack of phospholipid and apoprotein components, substantial protein leakage into the alveolar spaces occurs in the further course of RDS, which may significantly contribute to the deterioration of surfactant function [3, 4]. Moreover, augmented alveolar protein load, due to increased endothelial and epithelial permeability, represents one of the key events in the adult respiratory distress syndrome (ARDS) [5–8]. Blood, plasma and alveolar washings, obtained during states of severe plasma-leakage into the lung airspaces, were all noted to inhibit natural surfactant function [4, 9–12]. Accordingly, a variety of *in vitro* studies have demonstrated surfactant inhibiting properties of albumin [11, 13–15], haemoglobin [16] and, in particular, fibrinogen and fibrin monomer [11, 14, 15, 17–20].

Replacement therapy with a variety of natural surfactant extracts has proved beneficial in both experimental and clinical studies in RDS [1–3]. Differences in efficacy were, however, noted. These differences may be related to variations in the dosage of the material and the timing of administration (preventive *versus* rescue application). In addition, differences in the sensitivity of the various surfactant preparations to the inhibitory capacities of leaked proteins may be relevant in late RDS; and such differences will, supposedly, be critical for surfactant replacement in ARDS. In the present study, we compared the effects of plasma proteins with established surfactant-inhibitory properties on different surfactant preparations, all used in clinical replacement studies, and on a synthetic apoprotein-based phospholipid mixture. Marked differences in "protein sensitivity" were noted, which may have an impact on surfactant function under conditions of increased alveolar protein load.

Materials and Methods

Natural surfactant preparations

The following organic solvent surfactant extracts, all used in RDS replacement studies, were generously supplied for the current investigation: calf lung surfactant extract (CLSE) (provided by R.H. Notter) [21, 22]); Curosurf (pig lung surfactant extract; provided by B. Robertson, Stockholm, Sweden and Chiesi Pharmaceuticals, Parma, Italy) [23, 24]; Survanta (bovine lung surfactant extract, supplemented with dipalmitoylphosphatidylcholine, palmitic acid and tripalmitin; provided from Abbott, Wiesbaden, Germany) [25, 26]; Alveofact (bovine lavage surfactant extract; provided from B. Disse, Boehringer/Ingelheim, Germany) [27, 28].

Apoprotein-based synthetic surfactant

A synthetic phospholipid mixture (PLM) was prepared from dipalmitoylphosphatidylcholine (DPPC) (68.5%), egg phosphatidylglycerol (PG) (22.5%) and palmitic acid (PA) (9% wt/wt) according to TANAKA *et al.* [29]. To receive a synthetic apoprotein-based surfactant preparation with surface properties corresponding to natural surfactant preparations, this mixture was enriched with both natural bovine surfactant protein ($SP\text{-}B_{nat}$) (1% wt/wt) and non-palmitoylated human recombinant surfactant protein C ($SP\text{-}C_{rec}$) (2% wt/wt) as described previously [30]. The amino acid sequence of the recombinant SP-C is identical to that reported by other others [31–33]. This mixture will henceforth be referred to as PLM-C/B.

Surface tension measurements

All surfactant preparations were diluted with saline containing 3 mM calcium to the appropriate phospholipid concentrations directly before experimental use. For establishing dose-effect curves, the diluted preparations were vortexed for 1 min, and gently shaken for 30 min at 37°C, before performing bubble studies. To assess the inhibitory effect of different proteins, fibrinogen (Kabi-Vitrum, Stockholm, Sweden; 95% purity), albumin (Sigma, Munich, Germany; 98% purity), or haemoglobin (Sigma, Munich, Germany; 98% purity), were admixed to the surfactant preparations in a small volume of calcium containing saline (albumin, haemoglobin), or as lyophilized protein (fibrinogen) 25 min after vortexing. The final phospholipid concentration of this mixture was then 2 $mg \cdot ml^{-1}$, and the protein concentrations varied between 1 and 8 $mg \cdot ml^{-1}$. The mixture was sonicated for 1 min (20 kHz, 50 W Bandelin Sonopuls HD 60), and gently shaken for another 5 min, before performing surface tension measurements.

The oscillating bubble technique was applied as described previously [34], using a pulsating bubble surfactometer (Electronetics Co., Amherst, NY, USA). After the 30 min incubation period, the surfactant material was transferred to the disposable sample chamber. A bubble of minimal radius (r=0.4 mm) was automatically created at 37°C, and while the bubble was not pulsating but maintained at that minimal size, pressure was continuously recorded for 12 s. Initially, the surface tension values at 2, 4, 6, 8, 10 and 12 s were taken to characterize adsorption rate. However, no additional information was obtained by such multiple point characterization of adsorption kinetics, and therefore only the 12 s values (γ_{ads}; given in $mN \cdot m^{-1}$) were used for final evaluation of data. Next, pulsation was started at a cycling rate of 20 $cycles \cdot min^{-1}$. The bubble radius then varied between 0.4–0.55 mm. Using the Laplace equation $p=2 \times \gamma/r$, the surface tension was calculated continuously with a microprocessor. The minimal surface tension (γ_{min}) was read after 5 min of oscillation at minimal bubble radius.

Analysis of phospholipid classes and SP-B

Lipids were extracted from the surfactants used in this study, according to the method of BLIGH and DYER [35]. The phospholipid classes were separated by high performance thin-layer chromatography, using silica gel 60 plates (Merck, Darmstadt, FRG). Samples (30 µg) were applied with a Linomat IV applicator (Camag, Muttenz, Switzerland). Chloroform:methanol:acetic acid:distilled water (50:37.5:3.5:2; vol/vol) was used as the mobile phase, and the phospholipids were stained with molybdenum blue reagent according to GUSTAVSSON [36], and quantified by densitometric scanning at 700 nm with TLC-Scanner II (Camag, Muttenz, Switzerland).

SP-B was quantified by a solid phase enzyme-linked immunosorbent assay (ELISA) technique (W. Seeger, G. Becker, H.J. Krämer and A. Günther; manuscript in preparation).

Statistics

For measuring statistical differences, two-way analyses of variance were performed.

Results

Biochemical analysis

The phospholipid profiles of the different natural surfactant preparations are given in table 1. All contained phosphatidylcholine percentages between 74–90%; however, marked differences were noted in the smaller phospholipid fractions. The phosphatidylglycerol contents varied between 1–9%, those of lysophosphatidylcholine between 0–7%, and significant quantities of sphingomyelin were detected in Curosurf and Survanta, but not in Alveofact and CLSE. Similarly, considerable variation in SP-B contents was observed. Related to the total amount of phospholipids (wt/wt), the SP-B was measured to be 1.7% in the CLSE and Alveofact preparations used, 0.2% in Curosurf and <0.1% in Survanta.

Table 1. – Phospholipid classes of natural surfactant preparations*

	PC	LPC	SPH	PI	PE	PG	CL
Survanta	87.2 ±1.2	2.2 ±0.2	4.8 ±0.8	0.5 ±0.1	2.2 ±0.3	3.2 ±0.2	ND
Alveofact	82.0 ±1.4	4.0 ±0.2	1.4 ±0.3	0.5 ±0.2	3.0 ±0.4	9.0 ±1.3	ND
CLSE	89.3 ±1.1	ND	1.4 ±0.3	2.5 ±0.5	2.5 ±0.3	3.6 ±0.3	0.8 ±0.2
Curosurf	74.5 ±0.8	6.9 ±0.7	8.1 ±0.8	3.3 ±0.4	4.5 ±0.6	1.2 ±0.3	ND ND

*: Phospholipids were quantified as detailed in Materials and Methods. Mean values (n=5) ±SD of each phospholipid class are given in percentage of total phospholipid. PC: phosphatidylcholine; LPC: lysophosphatidylcholine; SPH: sphingomyelin; PI: phosphatidylinositol; PE: phosphatidy-lethanolamine; PG: phosphatidylglycerol; CL: cardiolipin; ND: not detectable; CLSE: calf lung surfactant extract.

0.5 mg·ml^{-1} and by CLSE at 1 mg·ml^{-1} phospholipids. In accordance with these differences in the dose-effect curves, near zero γ_{min} data were reached within <3 bubble pulsations at 2 mg·ml^{-1} PLM-C/B, and within <10 oscillations at 2 mg·ml^{-1} CLSE in all experiments, whereas >1 min of pulsation was necessary to achieve such low surface tension upon use of 2 mg·ml^{-1} Curosurf or Alveofact. Survanta displayed γ_{min} values of ≈4 mN·m^{-1} at 2 mg·ml^{-1} lipids; additional experiments showed that >5 mg·ml^{-1} of this surfactant preparation was necessary to establish near zero surface tension in the bubble surfactometer (data not given in detail).

Sensitivity to protein inhibition

Marked differences in the sensitivity to surfactant inhibitory proteins were displayed by the various surfactant preparations (figs. 2–4). Both adsorption kinetics and dynamic surface tension lowering properties of CLSE and Alveofact were only moderately affected by fibrinogen up

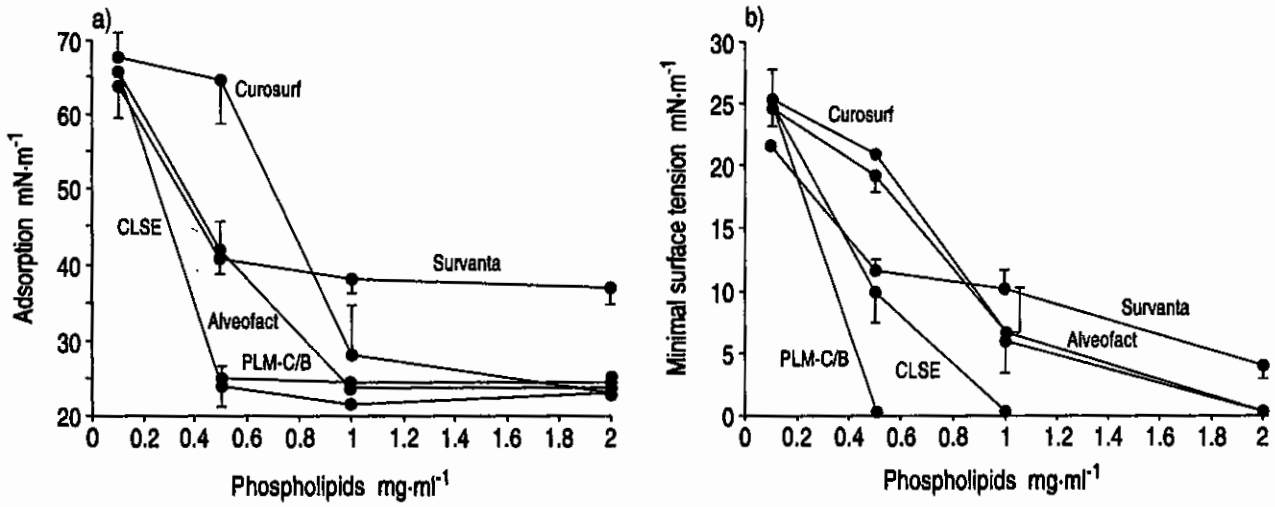

Fig. 1. – a) Dose-dependent adsorption facilities (γ_{ads}) read after 12 s); and b) dose-dependent dynamic surface tension lowering properties (γ_{min}) after 5 min oscillation, of different surfactant preparations. Mean±SEM of at least five experiments each are given. SEM bars are missing when falling into symbol. PLM-C/B: apoprotein C- and B-based phospholipid-fatty acid mixture; CLSE: calf lung surfactant extract.

Baseline biophysical properties

Dose-dependency of adsorption kinetics was displayed by all surfactant preparations within the currently used range of phospholipid concentrations (fig. 1). With the exception of Survanta, all γ_{ads} values at 2 mg·ml^{-1} phospholipids ranged between 20–25 mN·m^{-1}. Similar rapid adsorption was achieved by CLSE and PLM-C/B at only 0.5 mg·ml^{-1} lipids, and by Alveofact at 1 mg·ml^{-1}. γ_{ads} values of Survanta did not fall below 35 mN·m^{-1} at any of the phospholipid concentrations used.

At 2 mg·ml^{-1} phospholipids, PLM-C/B, CLSE, Curosurf and Alveofact achieved near zero surface tension within the 5 min bubble oscillation period (fig. 1). Such low γ_{min} values were reached by PLM-C/B at only

to 8 mg·ml^{-1}, and both surfactant preparations were virtually unaffected by albumin and haemoglobin up to corresponding protein concentrations. In contrast, Curosurf and Survanta were markedly inhibited by all three proteins, both with respect to adsorption facilities and minimal surface tension upon bubble oscillation. Only 1 mg·ml^{-1} fibrinogen sufficed to raise the γ_{ads} values to nearly 50 mN·m^{-1}; and at 4 mg·ml^{-1} of all proteins, γ_{min} data of Curosurf and Survanta ranged above 20 mN·m^{-1}. PLM-C/B displayed differential sensitivity to the various proteins. This synthetic mixture was only moderately affected by fibrinogen, it showed intermediate sensitivity to albumin and was markedly inhibited by haemoglobin, both in terms of adsorption kinetics and dynamic surface tension lowering properties.

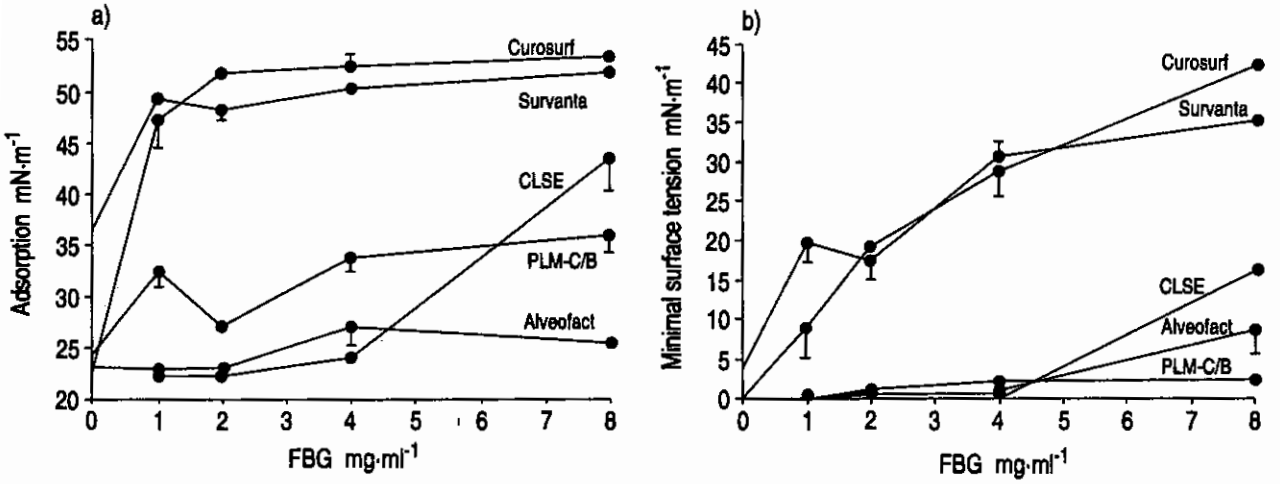

Fig. 2. – Dose-related influence of fibrinogen (FBG): a) on adsorption kinetics; and b) on dynamic surface tension lowering properties, of different surfactant preparations. All surfactants were used at 2 mg·ml^{-1} phospholipids. Mean±SEM of at least five experiments each are given. SEM bars are missing when falling into symbol. Curosurf and Survanta differ from CLSE, PLM-C/B, or Alveofact ($p<0.001$). For abbreviations see legend to figure 1.

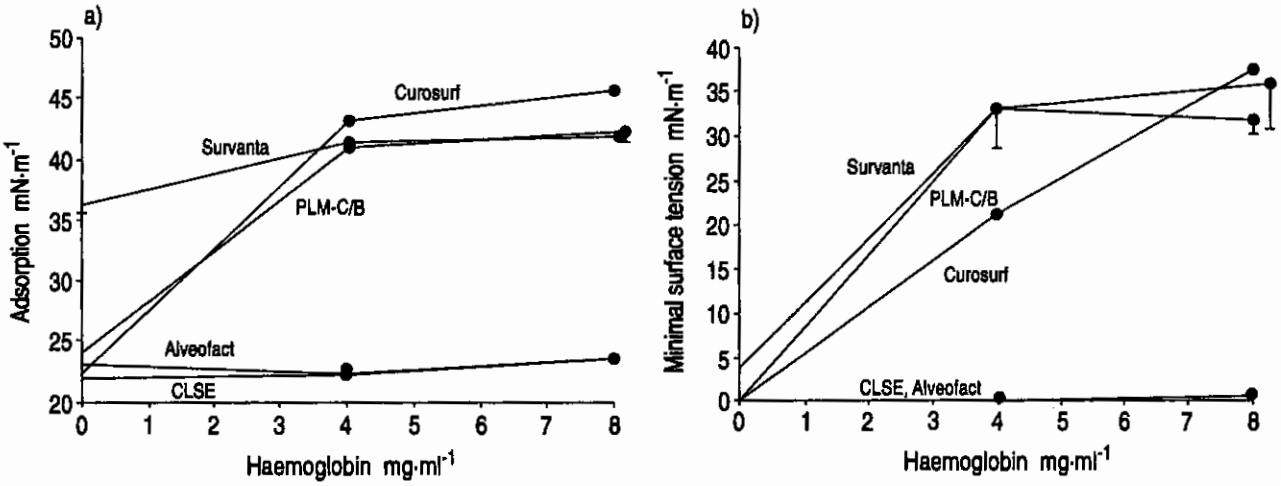

Fig. 3. – Dose-related influence of haemoglobin: a) on adsorption kinetics; and b) dynamic surface tension lowering properties, of different surfactant preparations, All surfactants were used at 2 mg·ml^{-1} phospholipids. Mean±SEM of at least five experiments each are given. SEM bars are missing when falling into symbol. Curosurf, Survanta and PLM-C/B significantly differ from CLSE or Alveofact ($p<0.001$). For abbreviations see legend to figure 1.

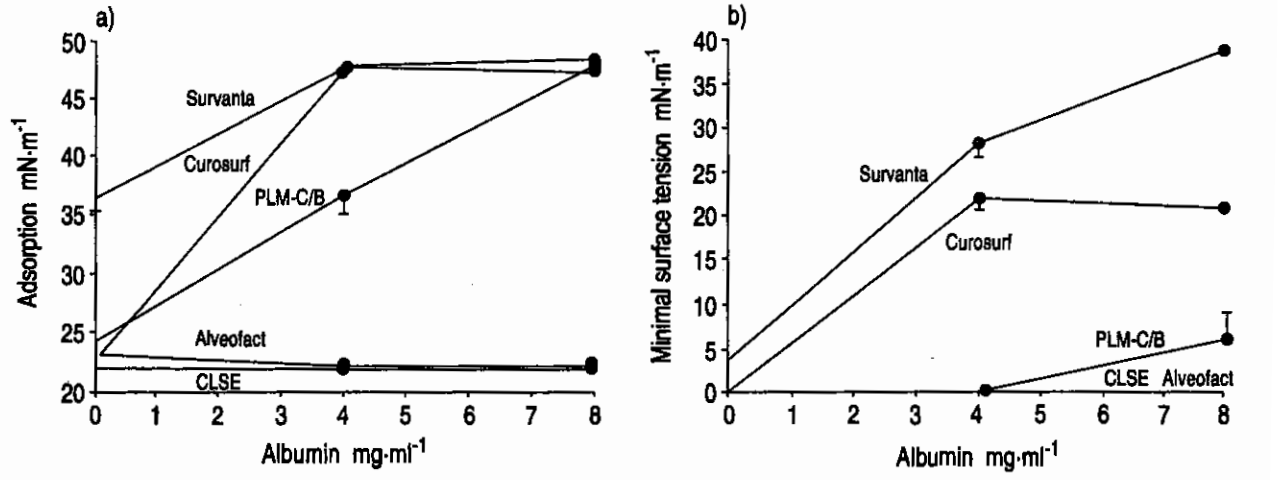

Fig. 4. – Dose-related influence of albumin: a) on adsorption kinetics; and b) on dynamic surface tension lower properties, of different surfactant preparations. All surfactants were used at 2 mg·ml^{-1} phospholipids. Mean±SEM of at least five experiments each are given. SEM bars are missing when falling into symbol. Curosurf and Survanta differ from CLSE or Alveofact with $p<0.001$. For abbreviations see legend to figure 1.

Discussion

The surface properties of the natural surfactant preparations CLSE, Alveofact and Curosurf meet generally accepted criteria of satisfying surfactant function. At 2 $mg \cdot ml^{-1}$, rapid adsorption was noted ($\gamma ads \approx 22–25$ $mN \cdot m^{-1}$), and near zero minimal surface tension was reached upon bubble oscillation within <3 min. The dose-response curves revealed a rank order of efficacy with CLSE > Alveofact > Curosurf, both with respect to adsorption facilities and dynamic surface tension lowering properties. Obviously, deviating surface properties were registered for Survanta in the presently used concentration range ($\gamma_{ads} \approx 36$ $mN \cdot m^{-1}$ and $\gamma_{min} \approx 4$ $mN \cdot m^{-1}$ at 2 $mg \cdot ml^{-1}$ phospholipids). These data correspond to previous investigations in this surfactant preparation [11, 25]; serial studies with higher strengths of Survanta in order to achieve lower γ_{ads} and γ_{min} values were not performed in the current study.

Since the discovery of the extreme hydrophobic surfactant apoproteins SP-B and SP-C, their essential role in adsorption and dynamic surface tension lowering facilities of alveolar surfactant has become increasingly evident [37–43]. In a preceding investigation, supplementation of a synthetic phospholipid mixture, composed according to TANAKA *et al.* [32], with both non-palmitoylated SP-C and SP-B, was optimized for assessment of high standard surface tension properties, including low sensitivity to the inhibitory capacity of fibrinogen [33]. The dose-effect curves of this synthetic material displayed similar (γ_{ads}), or even slightly higher (γ_{min}), relative efficacy as compared to CLSE, the most potent natural surfactant preparation presently studied.

In accordance with previous investigations [11, 14, 15, 17–20, 33, 44] fibrinogen caused dose-dependent inhibition of all natural surfactant preparations employed. Marked differences in the sensitivity to this inhibitory plasma protein were, however, noted. Whereas the surface activities of Curosurf and Survanta were severely deteriorated by low protein concentrations, a fibrinogen-phospholipid ratio of more than 2:1 was needed for significant inhibition of the surface properties of CLSE and Alveofact. In accordance with this differential sensitivity to fibrinogen, surface tension characteristics of Curosurf and Survanta were dose-dependently inhibited by albumin and haemoglobin, whereas these proteins exerted no significant effect on CLSE and Alveofact. As stated above, PLM-C/B was "designed" to achieve far-reaching resistance to the inhibitory capacity of fibrinogen, and was thus only slightly affected by this plasma protein. In contrast, haemoglobin severely deteriorated the surface activity of this synthetic surfactant mixture, and it displayed intermediate sensitivity to albumin. Several aspects may underlie these marked differences in protein sensitivity of the various surfactant preparations.

Firstly, variations in lipid composition. Comparing available data concerning the lipid composition of different surfactant preparations, HALLIDAY [45] considered the relative phospholipid content to be 84% (Survanta), 92% (CLSE) and 99% (Curosurf); for Alveofact, the phospholipids were reported to represent 88% of the lipids. Correspondingly, triglycerides and free fatty acids were noted to be virtually absent (Curosurf [46]), or to range up to ≈6% each (Survanta [25]). Cholesterol was missing in Curosurf [46], and Survanta [25], and was reported to range at ≈4% in CLSE [22] and Alveofact [47]. As detailed in table 1, marked differences in the phospholipid profiles were additionally noted, in particular with respect to the percentages of phosphatidylglycerol, sphingomyelin and lysophosphatidylcholine. These variations in the lipid composition of the different surfactant preparations must be assumed to influence their surface properties under baseline conditions, and in the presence of inhibitory proteins.

Secondly, variations in apoprotein composition. Since all natural surfactants underwent an organic solvent extraction procedure, no substantial quantities of surfactant protein A (SP-A) are present in these preparations. SP-B and SP-C are co-extracted with the lipids, and thus contained in these preparations; however, their ratio has hitherto only been reported for Curosurf (1:3, [46]). Quantification of the SP-B contents by ELISA technique revealed marked differences between the various surfactants, with CLSE and Alveofact containing high amounts (>1.5%, related to phospholipids), and Curosurf and Survanta containing low percentages (<0.25%) of this hydrophobic apoprotein. Interestingly, these differences correspond to the differential sensitivities to inhibitory proteins noted for the various surfactant preparations (high sensitivity of Curosurf and Survanta, low susceptibility of CLSE and Alveofact). Preceding studies in our laboratory showed that the fibrinogen inhibition of a recombinant SP-C based phospholipid mixture is markedly counteracted by supplementation with small amounts of SP-B. Conversely, the fibrinogen sensitivity of a natural surfactant preparation (CLSE) was found to be substantially increased by functional inhibition of SP-B with use of antibody [33]. The low sensitivity of the SP-C/B-based synthetic phospholipid mixture to fibrinogen was confirmed in the present study. Interestingly, however, this feature contrasted with a high sensitivity of the synthetic material towards the inhibitory capacity of haemoglobin, which suggests different underlying mechanisms of interference with surfactant function for these two proteins. Supplementation of an organic extract of bovine surfactant with SP-A was recently noted to counteract the inhibitory effect of fibrinogen [15]. Accordingly, SP-A enrichment of a solvent extracted bovine lavage material was reported to improve its functional activity in a preterm ventilated rabbit model, in which alveolar protein leakage is known to occur rapidly [48]. Altogether, these studies suggest that differences in the hydrophobic apoprotein contents, in particular SP-B, may have considerable impact on plasma protein sensitivities of natural and synthetic surfactant materials, and that this might be further modulated by additional supplementation with SP-A.

Thirdly, presence of contaminating materials. CLSE and Alveofact, which were extracted from lavage fluids, displayed low sensitivity to fibrinogen, and were resistant to haemoglobin and albumin, whereas Curosurf and Survanta, solvent extracted from minced lung tissues,

were severely inhibited by all three proteins. This may suggest co-extraction of compounds from the lung tissue, which are not present in the alveolar space assessed by lavage. Extracted membrane lipids and constituents of lung ground substance have been suggested as tissue-derived candidates with surfactant inhibitory properties [16, 20]. However, no definite data on putative contaminating material in the minced tissue extracts are presently available.

In conclusion, natural surfactant extracts, used for RDS replacement therapy, and an apoprotein-based synthetic phospholipid mixture displayed marked differences in their sensitivity to inhibitory plasma proteins. Such differences may have considerable impact on surfactant function under conditions of increased alveolar protein load, such as late RDS and ARDS. Further work will be necessary to relate the differential protein sensitivity to variations in surfactant apoprotein and/or lipid composition, or to putative co-extracted compounds.

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INFASURF ® (calfactant)
Intratracheal Suspension
Sterile Suspension for Intratracheal Use Only

Rx Only Rev. 03/18

DESCRIPTION

Infasurf® (calfactant) Intratracheal Suspension is a sterile, non-pyrogenic lung surfactant intended for intratracheal instillation only. It is an extract of natural surfactant from calf lungs which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C). It contains no preservatives.

Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 - 6.2 (target pH 5.7). Each milliliter of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.7 mg proteins including 0.26 mg of SP-B.

CLINICAL PHARMACOLOGY

Endogenous lung surfactant is essential for effective ventilation because it modifies alveolar surface tension thereby stabilizing the alveoli. Lung surfactant deficiency is the cause of Respiratory Distress Syndrome (RDS) in premature infants. Infasurf restores surface activity to the lungs of these infants.

Activity: Infasurf adsorbs rapidly to the surface of the air:liquid interface and modifies surface tension similarly to natural lung surfactant. A minimum surface tension of ≤3 mN/m is produced in vitro by Infasurf as measured on a pulsating bubble surfactometer. Ex vivo, Infasurf restores the pressure volume mechanics and compliance of surfactant-deficient rat lungs. In vivo, Infasurf improves lung compliance, respiratory gas exchange, and survival in preterm lambs with profound surfactant deficiency.

Animal Metabolism: Infasurf is administered directly to the lung lumen surface, its site of action. No human studies of absorption, biotransformation, or excretion of Infasurf have been performed. The administration of Infasurf with radiolabeled phospholipids into the lungs of adult rabbits results in the persistence of 50% of radioactivity in the lung alveolar lining and 25% of radioactivity in the lung tissue 24 hours later. Less than 5% of the radioactivity is found in other organs. In premature lambs with lethal surfactant deficiency, less than 30% of instilled Infasurf is present in the lung lining after 24 hours.

Clinical Studies: The efficacy of Infasurf was demonstrated in two multiple-dose controlled clinical trials involving approximately 2,000 infants treated with Infasurf (approximately 100 mg phospholipid/kg) or Exosurf Neonatal®. In addition, two controlled trials of Infasurf versus Survanta®, and four uncontrolled trials were conducted that involved approximately 15,500 patients treated with Infasurf.

Infasurf versus Exosurf Neonatal®

Treatment Trial

A total of 1,126 infants ≤72 hours of age with RDS who required endotracheal intubation and had an a/A PO_2 < 0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). Patients were given an initial dose and one repeat dose 12 hours later if intubation was still required. The dose was instilled in two aliquots through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated at 28 days or to discharge for all treated patients from this treatment trial are shown in Table 1.

Table 1- Infasurf vs Exosurf Neonatal®
Treatment Trial

Efficacy Parameter	Infasurf (N=570) %	Exosurf Neonatal® (N=556) %	p-Value
Incidence of air leaks [a]	11	22	≤0.001
Death due to RDS	4	4	0.95
Any death to 28 days	8	10	0.21
Any death before discharge	9	12	0.07
BPD [b]	5	6	0.41
Crossover to other surfactant [c]	4	4	1

[a] Pneumothorax and/or pulmonary interstitial emphysema.
[b] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[c] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 96 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10

Prophylaxis Trial

A total of 853 infants <29 weeks gestation were enrolled into a multiple-dose, randomized, double-blind prophylaxis trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). The initial dose was administered within 30 minutes of birth. Repeat doses were administered at 12 and 24 hours if the patient remained intubated. Each dose was administered divided in 2 equal aliquots, and given through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated to day 28 or to discharge for all treated patients from this prophylaxis trial are shown in Table 2.

Table 2- Infasurf vs Exosurf Neonatal®
Prophylaxis Trial

Efficacy Parameter	Infasurf (N=431) %	Exosurf Neonatal® (N=422) %	p-Value
Incidence of RDS	15	47	≤0.001
Incidence of air leaks [a]	10	15	0.01
Death due to RDS	2	5	≤0.01
Any death to 28 days	12	16	0.10
Any death before discharge	18	19	0.56
BPD [b]	16	17	0.60
Crossover to other surfactant [c]	0.2	3	<0.001

[a] Pneumothorax and/or pulmonary interstitial emphysema.
[b] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[c] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 72 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10

Infasurf versus Survanta®

Treatment Trial

A total of 662 infants with RDS who required endotracheal intubation and had an a/A PO_2 <0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). Repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Results for the major efficacy parameters evaluated at 28 days or to discharge (incidence of air leaks, death due to respiratory causes or to any cause, BPD, or treatment failure) for all treated patients from this treatment trial were not significantly different between Infasurf and Survanta®.

Prophylaxis Trial

A total of 457 infants ≤30 weeks gestation and <1251 grams birth weight were enrolled into a multiple-dose, randomized, double-blind trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). The initial dose was administered within 15 minutes of birth and repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral). Results for efficacy endpoints evaluated at 28 days or to discharge for all treated patients from this prophylaxis trial showed an increase in mortality from any cause at 28 days (p=0.03) and in death due to respiratory causes (p=0.005) in Infasurf-treated infants. For evaluable patients (patients who met the protocol-defined entry criteria), mortality from any cause and mortality due to respiratory causes were also higher in the Infasurf group (p = 0.07 and 0.03, respectively). However, these observations have not been replicated in other adequate and well-controlled trials and their relevance to the intended population is unknown. All other efficacy outcomes (incidence of RDS, air leaks, BPD, and treatment failure) were not significantly different between Infasurf and Survanta® when analyzed for all treated patients and for evaluable patients.

Acute Clinical Effects: As with other surfactants, marked improvements in oxygenation and lung compliance may occur shortly after the administration of Infasurf. All controlled clinical trials with Infasurf demonstrated significant improvements in fraction of inspired oxygen (F_iO_2) and mean airway pressure (MAP) during the first 24 to 48 hours following initiation of Infasurf therapy.

INDICATIONS AND USAGE

Infasurf is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment ("rescue") of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.

Prophylaxis

Prophylaxis therapy at birth with Infasurf is indicated for premature infants <29 weeks of gestational age at significant risk for RDS. Infasurf prophylaxis should be administered as soon as possible, preferably within 30 minutes after birth.

Treatment

Infasurf therapy is indicated for infants ≤72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

WARNINGS

Infasurf is intended for intratracheal use only.

THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING INFASURF, OFTEN RAPIDLY IMPROVES OXYGENATION AND LUNG COMPLIANCE. Following administration of Infasurf, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.

Infasurf therapy is not a substitute for neonatal intensive care. Optimal care of premature infants at risk for RDS and new born infants with RDS who need endotracheal intubation requires an acute care unit organized, staffed, equipped, and experienced with intubation, ventilator management, and general care of these patients.

TRANSIENT EPISODES OF REFLUX OF INFASURF INTO THE ENDOTRACHEAL TUBE, CYANOSIS, BRADYCARDIA, OR AIRWAY OBSTRUCTION HAVE OCCURRED DURING THE DOSING PROCEDURES. These events require stopping Infasurf administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing can proceed with appropriate monitoring.

PRECAUTIONS

When repeat dosing was given at fixed 12-hour intervals in the Infasurf vs. Exosurf Neonatal® trials, transient episodes of cyanosis, bradycardia, reflux of surfactant into the endotracheal tube, and airway obstruction were observed more frequently among infants in the Infasurf-treated group.

An increased proportion of patients with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was observed in Infasurf-treated infants in the Infasurf-Exosurf Neonatal® controlled trials. These observations were not associated with increased mortality.

No data are available on the use of Infasurf in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation.

Data from controlled trials on the efficacy of Infasurf are limited to doses of approximately 100 mg phospholipid/kg body weight and up to a total of 4 doses.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis studies and animal reproduction studies have not been performed with Infasurf. A single mutagenicity study (Ames assay) was negative.

ADVERSE REACTIONS

The most common adverse reactions associated with Infasurf dosing procedures in the controlled trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). These events were generally transient and not associated with serious complications or death.

The incidence of common complications of prematurity and RDS in the four controlled Infasurf trials are presented in Table 3. Prophylaxis and treatment study results for each surfactant are combined.

Table 3 - Common Complications of Prematurity and RDS in Controlled Trials

Complication	Infasurf (N=1001) %	Exosurf Neonatal® (N=978) %	Infasurf (N=553) %	Survanta® (N=566) %
Apnea	61	61	76	76
Patent ductus arteriosus	47	48	45	48
Intracranial hemorrhage	29	31	36	36
Severe intracranial hemorrhage[a]	12	10	9	7
IVH and PVL [b]	7	3	5	5
Sepsis	20	22	28	27
Pulmonary air leaks	12	22	15	15
Pulmonary interstitial emphysema	7	17	10	10
Pulmonary hemorrhage	7	7	7	6
Necrotizing enterocolitis	5	5	17	18

[a] Grade III and IV by the method of Papile.
[b] Patients with both intraventricular hemorrhage and periventricular leukomalacia.

Follow-up Evaluations

Two-year follow-up data of neurodevelopmental outcomes in 415 infants enrolled in 5 centers that participated in the Infasurf vs. Exosurf Neonatal® controlled trials demonstrated significant developmental delays in equal percentages of Infasurf and Exosurf Neonatal® patients.

OVERDOSAGE

There have been no reports of overdosage with Infasurf. While there are no known adverse effects of excess lung surfactant, overdosage would result in overloading the lungs with an isotonic solution. Ventilation should be supported until clearance of the liquid is accomplished.

DOSAGE AND ADMINISTRATION

FOR INTRATRACHEAL ADMINISTRATION ONLY

Infasurf should be administered under the supervision of clinicians experienced in the acute care of newborn infants with respiratory failure who require intubation. Rapid and substantial increases in blood oxygenation and improved lung compliance often follow Infasurf instillation. Close clinical monitoring and surveillance following administration may be needed to adjust oxygen therapy and ventilator pressures appropriately.

Dosage

Each dose of Infasurf is 3 mL/kg body weight at birth. Infasurf has been administered every 12 hours for a total of up to 3 doses.

Directions for Use

Infasurf is a suspension which settles during storage. Gentle swirling or agitation of the vial is often necessary for redispersion. DO NOT SHAKE. Visible flecks in the suspension and foaming at the surface are normal for Infasurf. Infasurf should be stored at refrigerated temperature 2° to 8°C (36° to 46°F). THE 3mL VIAL MUST BE STORED UPRIGHT. Date and time need to be recorded on the carton when Infasurf is removed from the refrigerator. Warming of Infasurf before administration is not necessary.

Unopened, unused vials of Infasurf that have warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Infasurf should not be removed from the refrigerator for more than 24 hours. **Infasurf should not be returned to the refrigerator more than once.** Repeated warming to room temperature should be avoided. Each single-use vial should be entered only once and the vial with any unused material should be discarded after the initial entry.

INFASURF DOES NOT REQUIRE RECONSTITUTION. DO NOT DILUTE OR SONICATE.

Dosing Procedures

General

Infasurf should only be administered intratracheally through an endotracheal tube. The dose of Infasurf is 3 mL/kg birth weight. The dose is drawn into a syringe from the single-use vial using a 20-gauge or larger needle with care taken to avoid excessive foaming. Administration is made by instillation of the Infasurf suspension into the endotracheal tube.

Administration for Treatment of RDS

When used to treat RDS, Infasurf may be administered using either of the following 2 methods:

Exosurf Active Control Trials: Initial and Repeat Dosing

In the Infasurf vs. Exosurf® trials, Infasurf was administered intratracheally through a side-port adapter into the endotracheal tube. Two attendants, one to instill the Infasurf, the other to monitor the patient and assist in positioning, facilitated the dosing. The dose (3 mL/kg) was administered in two aliquots of 1.5 mL/kg each. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Administration was made while ventilation was continued over 20-30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning separated the two aliquots. Repeat doses of 3 mL/kg of birth weight, up to a total of 3 doses 12 hours apart, were given if the patient was still intubated.

Survanta Active Control Trials: Initial and Repeat Dosing

In the Infasurf vs. Survanta® trials, Infasurf was administered through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a $P_aO_2 \leq 80$ torr.

Administration for Prophylaxis of RDS at Birth

Dosing procedures are described under Administration for Treatment of RDS. The amount of a prophylaxis dose of Infasurf should be based on the infant's birth weight. Administration of Infasurf for prophylaxis should be given as soon as possible after birth. Usually the immediate care and stabilization of the premature infant born with hypoxemia and/or bradycardia should precede Infasurf prophylaxis.

Dosing Precautions

During administration of Infasurf liquid suspension into the airway, infants often experience bradycardia, reflux of Infasurf into the endotracheal tube, airway obstruction, cyanosis, dislodgement of the endotracheal tube, or hypoventilation. If any of these events occur, the administration should be interrupted and the infant's condition should be stabilized using appropriate interventions before the administration of Infasurf is resumed. Endotracheal suctioning or reintubation is sometimes needed when there are signs of airway obstruction during the administration of the surfactant.

HOW SUPPLIED

Infasurf (calfactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered glass vials containing 3 mL (NDC 61938-456-03) and 6 mL (NDC 61938-456-06) off-white suspension.

Store Infasurf (calfactant) Intratracheal Suspension at refrigerated temperature 2° to 8°C (36° to 46°F) and protect from light. **THE 3 mL VIAL MUST BE STORED UPRIGHT.** Vials are for single use only. After opening, discard unused drug.

Rx only

Manufactured by:
ONY Biotech Inc.
Amherst, NY 14228

Rev. 03/18

Pharmacoeconomics in Surfactant Replacement Therapy

JPPT | Clinical Investigation

Comparison of the Pharmacoeconomics of Calfactant and Poractant Alfa in Surfactant Replacement Therapy

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OBJECTIVE To compare the pharmacy costs of calfactant (Infasurf, ONY, Inc.) and poractant alfa (Curosurf, Chiesi USA, Inc., Cary, NC).

METHODS The University of South Alabama Children's and Women's Hospital switched from calfactant to poractant alfa in 2013 and back to calfactant in 2015. Retrospectively, we used deidentified data from pharmacy records that provided type of surfactant administered, gestational age, birth weight, and number of doses on each patient. We examined differences in the number of doses by gestational ages and the differences in costs by birth weight cohorts because cost per dose is based on weight.

RESULTS There were 762 patients who received calfactant and 432 patients who received poractant alfa. The average number of doses required per patient was 1.6 administrations for calfactant-treated patients and 1.7 administrations for poractant alfa-treated patients, $p = 0.03$. A higher percentage of calfactant patients needed only 1 dose (53%) than poractant alfa patients (47%). The distribution of the number of doses for calfactant-treated patients was significantly lower than for the poractant alfa-patients, $p < 0.001$. Gestational age had no consistent effect on the number of doses required for either calfactant or poractant alfa. Per patient cost was higher for poractant alfa than for calfactant in all birth weight cohorts. Average per patient cost was $1160.62 for poractant alfa, 38% higher than the average per patient cost for calfactant ($838.34). Using poractant alfa for 22 months is estimated to have cost $202,732.75 more than it would have cost if the hospital had continued using calfactant.

CONCLUSION Our experience showed a strong pharmacoeconomic advantage for the use of calfactant compared to the use of poractant alfa because of similar average dosing and lower per patient drug costs.

ABBREVIATIONS FDA, Food and Drug Administration; GA, gestational age; RDS, respiratory distress syndrome;

KEYWORDS calfactant; Curosurf; Infasurf; pharmacoeconomics; poractant alfa; surfactant

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Introduction

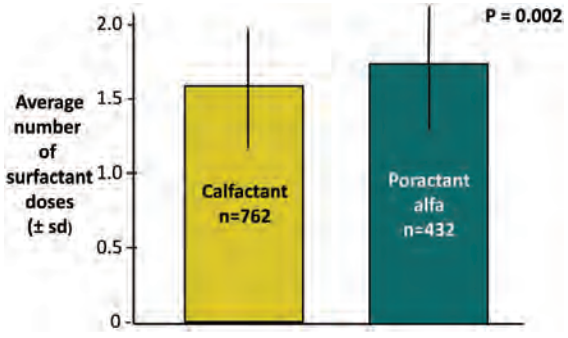
Currently there are 3 lung surfactant replacement products in the United States that are Food and Drug Administration (FDA) approved for treatment of newborn infants with respiratory distress syndrome (RDS), a severe and potentially fatal cause of respiratory failure in the first few days of life. Two of the products, calfactant (Infasurf; ONY, Inc., Amherst, NY) and beractant (Survanta; Abbvie, North Chicago, IL) are FDA approved for prevention of RDS (i.e., are indicated for therapy before any symptoms). Calfactant, beractant, and poractant alfa (Curosurf; Chiesi USA, Inc., Cary, NC) are FDA approved for treatment of RDS. Our institution used both poractant alfa and calfactant in the years between 2003 and 2011 and found no differences in the ultimate clinical outcomes of mortality, chronic lung disease, or acute pulmonary complications.

One of the advantages that the manufacturer claims for poractant alfa is that using its surfactant results in only a small percentage of patients requiring more than 1 dose.[1] The expectation that University of South Alabama Children's Hospital would experience a similarly reduced frequency of single dose usage was one of the factors that led us to change from calfactant to poractant alfa in 2013. We used poractant alfa exclusively for the next 22 months but did not observe a reduction in the rate of multiple doses needed in our patients. In 2015, we returned to using calfactant. This report describes the patterns of dosing in neonatal patients before, during, and after the switch from calfactant to poractant alfa and back to calfactant, as well as the pharmacoeconomic impact of those dosing patterns.

Materials and Methods

The data from the pharmacy records of University of South Alabama Children's Hospital provided the birth weight, gestational age (GA), and number of surfactant doses administered to each patient from February 2010

Figure 1. Comparison of the average number of doses of calfactant and poractant alfa.



through February 2016, a 6-year period. USA Children's & Women's Hospital delivers 3000 patients per year, and the neonatal intensive care unit (NICU) is a 70-bed level IIIB unit with over 1000 admissions per year. We included all patients who were treated with surfactant. Poractant alfa was the surfactant used from July 24, 2013, to June 7, 2015. Calfactant was used before and after the poractant alfa era. No patient identifiable data were used.

Both surfactants are suspensions in saline and stored refrigerated. A key difference is the cost to the institution derived from the number of single-dose vials used per patient and the price of those vials. An initial and a repeat dose of calfactant are the same 105 mg/kg (3 mL/kg) body weight. Calfactant comes in 3- and 6-mL vials. The number of vials of calfactant needed per dose is a single 3-mL vial for patients ≤1 kg, a single 6-mL vial for patients 1.001 to 2 kg, and a combination of vials for patients >2 kg. Poractant alfa dosing is more complex because the initial dose is 200 mg/kg (2.5 mL/kg), but repeat doses are 100 mg/kg (1.25 mL/kg). Poractant alfa comes in 1.5- and 3-mL vials. For initial doses, the number of vials of poractant alfa is a single 1.5-mL vial for patients ≤0.6 kg, a single 3-mL vial for patients 0.601 to 1.2 kg, and a combination of vials for patients >1.2 kg. For repeat doses, the number of vials of poractant alfa required is a single 1.5-mL vial for patients ≤1.25 kg, a single 3.0-mL vial for patients 1.2501 to 2.5 kg, and a combination of vials for patients >2.5 kg.

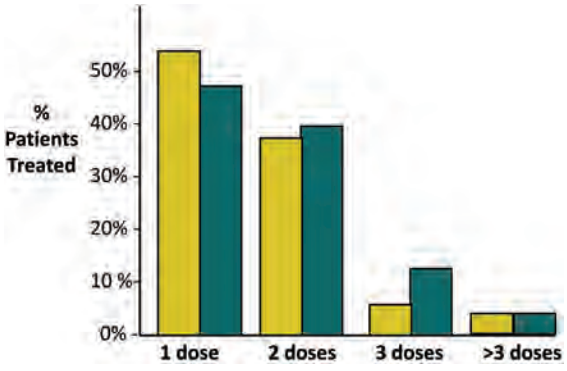
Costs are presented as the amount paid by the hospital per vial when describing the actual per patient costs and "as if" when we calculated what the difference in costs would have been had we continued to use calfactant during the 22 months when poractant alfa was used.

Comparisons between the surfactants used unpaired t tests and χ^2 distributions. A p value of < 0.05 was used as indicating a significant difference.

Results

During the 72 months, we reviewed charts of 1194 patients who received surfactant therapy, an average of 16.6 per month. Calfactant was administered to 762 patients over 50 months, an average of 15.2 per month; poractant alfa was administered to 432 patients over 22 months, an average of 19.6 per month. The average number of doses of calfactant was 1.6 per patient, slightly, but significantly, fewer than the 1.7 dose per patient for poractant alfa (Figure 1).

Figure 2. Distribution of the total number of doses required for calfactant and poractant alfa. The calfactant dose distribution is significantly less than the poractant alfa distribution: χ^2, 16.8; p = 0.0008.



A higher percent of patients received a single dose of calfactant, 53%, than poractant alfa patients, 47%; (Figure 2). A higher percentage of patients treated with poractant alfa required 2 or 3 total doses than calfactant-treated patients, and an equal percentage of patients in each treatment group received more than 3 doses. The difference in distribution of the number of doses is statistically significant, p = 0.0008.

The average number of doses per patient was examined among the different GA groups (Table 1). GA was unavailable for 7 (1.6%) of poractant alfa-treated patients and for 15 (2.0%) of calfactant-treated patients. GA for the total study population was not significantly correlated with the average number of doses for either calfactant or poractant alfa. The average number of doses was significantly higher in calfactant patients in the <24-week GA group and significantly lower in the 29- to 32-week GA group. The average number of calfactant doses per patient was equal to or lower than the number of poractant alfa doses per patient in the other GA groups.

Birth weight determines the size and number of vials needed for each dose of the surfactants. Birth weight was not available for 4 (0.9%) of the poractant alfa-treated patients and for 8 (1.0%) of the calfactant-treated patients. Table 2 shows the average vial usage per patient and the average cost per patient for that usage for each birth weight cohort. For calfactant, initial and retreatment doses are the same; for poractant alfa, a repeat dose is half the amount of the initial dose and

Table 1. Comparison of the Average Number of Doses per Patient in Gestational Age Cohorts

Gestational Age, wk	Poractant Alfa			Calfactant			p value
	n	Percent	Average Dose	n	Percent	Average Dose	
<24	59	14	1.4	86	12	1.7	0.008
24–25	58	13	1.4	91	12	1.5	0.323
26–28	109	25	1.5	174	23	1.5	1.000
29–32	123	28	2.0	195	26	1.3	< 0.001
33–37	62	14	2.0	180	24	2.0	1.000
≥38	14	3	2.7	21	3	1.9	0.071
Total	425	100	1.7	747	100	1.6	0.018

that difference is accounted for in the calculations of the average cost per patient. Per patient costs were lower for calfactant in all birth weight cohorts. The average per patient cost of poractant alfa was $1160.62 and for calfactant $838.34. Using poractant alfa averaged an increase of $322.28 over using calfactant, an increase of 38.4% per patient.

Since the patient mix was similar, but not identical, during the periods when the 2 surfactants were used, we compared the actual per patient costs that the hospital experienced during the 22 months during which poractant alfa was exclusively used to the projected surfactant costs if we had used calfactant for those patients instead (Table 3). We calculated that use of poractant alfa increased drug costs by $477.02 per patient or a total of $202,732.75 during the poractant alfa usage.

Discussion

In the management of the formulary of an institution, economics become important when multiple options are available for pharmaceutical products with equivalent effectiveness, side effects, and safety. A large, greater than 50,000 patients, retrospective study identified no difference in efficacy outcomes of survival and bronchopulmonary dysplasia or safety outcomes related to the use of beractant, calfactant, or poractant alpha.[1] We also retrospectively examined outcomes in our surfactant-treated population after changing from calfactant to poractant alpha in 2012 and observed no improvement in survival and no decrease in the incidence of bronchopulmonary dysplasia or other major complications of prematurity.[2]

Chiesi USA, the marketer of poractant alfa, promotes a very low rate of multiple doses, only 12% to 27% of patients requiring multiple doses in the 5 studies cited on their website[3] and replicated in Figure 3.[4–8] During the period of this report, the decision to retreat a patient, and how often retreatment was necessary, was at the discretion of the clinician responsible for the care of the patient and was not guided by a rigid protocol. The change to poractant alfa in our institution did not result in a decrease in the average doses per patient or the total doses used in the NICU, nor did the percentage of our patients requiring only a single dose approach the

Table 2. The Mean Number of 1.5- and 3.0-mL Vials of Poractant Alfa Used per Patient and the Average per Patient Cost of Those Vials and the Mean Number of 3.0- and 6.0-mL Vials of Calfactant Used per Patient and the Average per Patient Cost of Those Vials

Birth Weight Cohorts, g	Poractant Alfa				Calfactant			
	n	1.5 mL	3 mL	Average Patient Cost in USD	n	3 mL	6 mL	Average Patient Cost*
<500	50	1.5	0	442.62	58	1.5	0	429.05
500–999	156	0.6	0.8	624.68	245	1.5	0	417.45
1000–1499	81	0.8	1.6	1112.50	154	0	1.3	647.43
1500–1999	68	0.7	2.5	1611.32	94	0	1.3	624.74
2000–2499	29	0.2	2.8	1641.50	87	2.0	2.0	1506.21
2500–2999	16	2.4	3.4	2842.40	60	2.2	2.2	1648.59
≥3000	28	1.3	4.7	3081.34	56	0.2	4.0	2075.02
Total	428	0.9	1.6	1160.62	754	0.9	1.2	838.34

USD, United States dollars

Table 3. Comparison of Differences in Total Cost of Surfactant by Birthweight Cohort if Calfactant Had Been Used at USA Children's & Women's Hospital Between July 24, 2013, and June 7, 2015, When Poractant Alfa Was Actually Used

Birth Weight Cohorts, g	n	Actual per Patient Cost in USD: Poractant Alfa	Calculated per Patient Cost in USD: Calfactant*	Different in Cost per Cohort
<500	50	459.78	409.50	2514.00
500–999	156	640.54	409.50	36,042.24
1000–1499	81	1137.62	629.20	41,182.02
1500–1999	68	1644.50	629.20	69,040.04
2000–2499	29	1728.64	1514.00	6224.56
2500–2999	16	2667.43	1665.40	16,032.48
>3000	28	3122.65	1990.60	31,697.40
Total	428			202,732.75

USA, University of South Alabama; USD, United States dollars

* Calculation of calfactant cost uses dosing experience presented in Table 2 for each birth weight cohort.

range promoted for poractant alfa. We reviewed each of the studies cited in Figure 3 to try to identify factors that made single dosing so much more common than in our own experience with poractant alfa. Two of the studies in Figure 3 compared poractant alfa to another surfactant, beractant, Dizdar et al[4] and Ramanathan et al.[7] The other 3 were examining alternative methodologies for dosing poractant alfa. All of the studies cited in Figure 3 were complex, randomized controlled trials and were a small select population whose supervision and management may have been different from patients who were not recruited into the clinical trial. Four of the studies recruited between 0.3 and 1.1 patients per site per month. Only Dizdar et al[4] had a larger rate of inclusion of 8.8 patients per month at its single site.

Single dose success rates vary among centers and published studies. A low rate of single dosing of poractant alfa, 37%, was reported in a large, prospective single site study of 415 surfactant-treated patients in which poractant alfa and beractant were used in alternating months.[9] A large, 2168-patient multicenter poractant alfa study, published more than 2 decades ago, comparing 200 mg/kg dose of poractant alfa to a 100-mg/kg dose, reported only 31% of the high dose patients required a single dose.[10] However, a more recent study by Jeon et al[11] reported consecutive periods of surfactant use of 3 different surfactants, poractant alfa, calfactant, and beractant, which included all surfactant-treated patients at a single site treating 6.9 patients per month and observed a high rate of single dosing for 3 surfactants: poractant alfa, 77%; calfactant, 83%; and beractant, 83%.[11]

The failure to observe high rate of single dosing is not unique to our study. The rate of single dosing appears to depend on the site, not the surfactant. The similarity of the pattern of usage between calfactant and poractant alfa observed in this report replicates 1 of the 2 previous reports comparing the usage between these 2 surfactants. In addition to Jeon et al,[11] Gerdes et al[12] reported calfactant patients averaging 1.72 doses and poractant alfa patients averaging 1.67 doses.[12] The Gerdes et al[12] experience is almost identical to the average per patient dosing of 1.6 for calfactant patients and 1.7 for poractant alfa patients observed in this experience.

A pharmacoeconomic advantage for poractant alfa over calfactant was advanced by Gerdes et al[12] because they observed a difference of 1.6 minutes in the average time to administer a dose, converting this spared time to a decreased administration cost of $0.79 per patient. In their results, they identified more "wastage" of calfactant, defined as the amount of material in a single-dose vial that was not used compared to poractant alfa. However, in their discussion they stated that the difference in wastage was not statistically different when calfactant use included both a 3-mL and a 6-mL vial. Both products are presented in single-use vials and this "wasted" amount cannot be used for future doses. Gerdes et al[12] did not report an actual quantitative comparison of the cost of the surfactants because their institutional costs were unavailable for analysis. The fact that the average number of doses per patient was 1.67 for poractant alfa and 1.72 for calfactant and the absence of cost of drug data make their conclusion of a possible pharmacoeconomic advantage for poractant alfa over calfactant unsupported by appropriate data.

The calculation of the cost per patient in this experience shows what is inevitable if the usage per patient is similar with calfactant or poractant alfa—the costs per patient are going to be determined by the difference in price between the 2 products. Poractant alfa requires more drug, 200 mg/kg versus 105 mg/kg for the first dose, so even though the cost when calculated on a per milligram of surfactant is almost similar, the cost for the first dose is much higher using poractant alfa than calfactant. The costs of repeat doses of calfactant and

Figure 3. Partial reproduction of poractant alfa promotional data on single-dose success on its website in April 2017.

CUROSURF demonstrates consistently high rates of single-dose success

Single-dose success in clinical studies

CLINICAL STUDY	N*	GESTATIONAL AGE	CUROSURF (200 mg/kg) SINGLE-DOSE SUCCESS†
Dizdar EA, et al. 2011[4]	126	Median 28 wks	88%
Sandri F, et al. 2010 (treatment arm)[5]	103	Mean 27.0 ± 1.0 wks	78%
Dani C, et al. 2004[6]	27	<30 wks	74%
Ramanathan R, et al.2004[7]	293	Mean 28.7 ± 2.0 wks	73%
Verder H, et al. 1999[8]	60	25-29 wks	88%

* Total number of infants randomized

† Single dose success is defined as no need for repeat doses of Curosurf®(poractant alfa)

poractant alfa are more similar because the amount of the repeat dose in mg/kg is similar. For a hospital with a low rate of multiple dosing, the cost differential between calfactant and poractant alfa will be greater than observed here because a higher percentage of the doses administered will be initial doses, not repeat doses.

Conclusions

The single-site data presented here show a strong pharmacoeconomic advantage for calfactant compared to poractant alfa. The reason for the higher cost of poractant alfa is because its initial dose of 200 mg/kg is almost twice as large as the initial 105-mg/kg dose of calfactant.

We did not observe the promotional claim, "consistently high rates of single dose success," with poractant alfa. Single-dosing rates for both calfactant and poractant alfa vary substantially in the available literature. This is the third comparison of poractant alfa and calfactant dosing in which the rate of single dose and/or average number of doses is similar.

ARTICLE INFORMATION

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INFASURF ® (calfactant)
Intratracheal Suspension
Sterile Suspension for Intratracheal Use Only

Rx Only Rev. 03/18

DESCRIPTION

Infasurf® (calfactant) Intratracheal Suspension is a sterile, non-pyrogenic lung surfactant intended for intratracheal instillation only. It is an extract of natural surfactant from calf lungs which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C). It contains no preservatives.

Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 - 6.2 (target pH 5.7). Each milliliter of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.7 mg proteins including 0.26 mg of SP-B.

CLINICAL PHARMACOLOGY

Endogenous lung surfactant is essential for effective ventilation because it modifies alveolar surface tension thereby stabilizing the alveoli. Lung surfactant deficiency is the cause of Respiratory Distress Syndrome (RDS) in premature infants. Infasurf restores surface activity to the lungs of these infants.

Activity: Infasurf adsorbs rapidly to the surface of the air:liquid interface and modifies surface tension similarly to natural lung surfactant. A minimum surface tension of ≤3 mN/m is produced in vitro by Infasurf as measured on a pulsating bubble surfactometer. Ex vivo, Infasurf restores the pressure volume mechanics and compliance of surfactant-deficient rat lungs. In vivo, Infasurf improves lung compliance, respiratory gas exchange, and survival in preterm lambs with profound surfactant deficiency.

Animal Metabolism: Infasurf is administered directly to the lung lumen surface, its site of action. No human studies of absorption, biotransformation, or excretion of Infasurf have been performed. The administration of Infasurf with radiolabeled phospholipids into the lungs of adult rabbits results in the persistence of 50% of radioactivity in the lung alveolar lining and 25% of radioactivity in the lung tissue 24 hours later. Less than 5% of the radioactivity is found in other organs. In premature lambs with lethal surfactant deficiency, less than 30% of instilled Infasurf is present in the lung lining after 24 hours.

Clinical Studies: The efficacy of Infasurf was demonstrated in two multiple-dose controlled clinical trials involving approximately 2,000 infants treated with Infasurf (approximately 100 mg phospholipid/kg) or Exosurf Neonatal®. In addition, two controlled trials of Infasurf versus Survanta®, and four uncontrolled trials were conducted that involved approximately 15,500 patients treated with Infasurf.

Infasurf versus Exosurf Neonatal®

Treatment Trial

A total of 1,126 infants ≤72 hours of age with RDS who required endotracheal intubation and had an a/A PO_2 < 0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). Patients were given an initial dose and one repeat dose 12 hours later if intubation was still required. The dose was instilled in two aliquots through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated at 28 days or to discharge for all treated patients from this treatment trial are shown in Table 1.

Table 1- Infasurf vs Exosurf Neonatal®
Treatment Trial

Efficacy Parameter	Infasurf (N=570) %	Exosurf Neonatal® (N=556) %	p-Value
Incidence of air leaks [a]	11	22	≤0.001
Death due to RDS	4	4	0.95
Any death to 28 days	8	10	0.21
Any death before discharge	9	12	0.07
BPD [b]	5	6	0.41
Crossover to other surfactant [c]	4	4	1

[a] Pneumothorax and/or pulmonary interstitial emphysema.
[b] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[c] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 96 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10

Prophylaxis Trial

A total of 853 infants <29 weeks gestation were enrolled into a multiple-dose, randomized, double-blind prophylaxis trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). The initial dose was administered within 30 minutes of birth. Repeat doses were administered at 12 and 24 hours if the patient remained intubated. Each dose was administered divided in 2 equal aliquots, and given through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated to day 28 or to discharge for all treated patients from this prophylaxis trial are shown in Table 2.

Table 2- Infasurf vs Exosurf Neonatal®
Prophylaxis Trial

Efficacy Parameter	Infasurf (N=431) %	Exosurf Neonatal® (N=422) %	p-Value
Incidence of RDS	15	47	≤0.001
Incidence of air leaks [a]	10	15	0.01
Death due to RDS	2	5	≤0.01
Any death to 28 days	12	16	0.10
Any death before discharge	18	19	0.56
BPD [b]	16	17	0.60
Crossover to other surfactant [c]	0.2	3	<0.001

[a] Pneumothorax and/or pulmonary interstitial emphysema.
[b] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[c] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 72 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10

Infasurf versus Survanta®

Treatment Trial

A total of 662 infants with RDS who required endotracheal intubation and had an a/A PO_2 <0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). Repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Results for the major efficacy parameters evaluated at 28 days or to discharge (incidence of air leaks, death due to respiratory causes or to any cause, BPD, or treatment failure) for all treated patients from this treatment trial were not significantly different between Infasurf and Survanta®.

Prophylaxis Trial

A total of 457 infants ≤30 weeks gestation and <1251 grams birth weight were enrolled into a multiple-dose, randomized, double-blind trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). The initial dose was administered within 15 minutes of birth and repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral). Results for efficacy endpoints evaluated at 28 days or to discharge for all treated patients from this prophylaxis trial showed an increase in mortality from any cause at 28 days (p=0.03) and in death due to respiratory causes (p=0.005) in Infasurf-treated infants. For evaluable patients (patients who met the protocol-defined entry criteria), mortality from any cause and mortality due to respiratory causes were also higher in the Infasurf group (p = 0.07 and 0.03, respectively). However, these observations have not been replicated in other adequate and well-controlled trials and their relevance to the intended population is unknown. All other efficacy outcomes (incidence of RDS, air leaks, BPD, and treatment failure) were not significantly different between Infasurf and Survanta® when analyzed for all treated patients and for evaluable patients.

Acute Clinical Effects: As with other surfactants, marked improvements in oxygenation and lung compliance may occur shortly after the administration of Infasurf. All controlled clinical trials with Infasurf demonstrated significant improvements in fraction of inspired oxygen (F_iO_2) and mean airway pressure (MAP) during the first 24 to 48 hours following initiation of Infasurf therapy.

INDICATIONS AND USAGE

Infasurf is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment ("rescue") of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.

Prophylaxis

Prophylaxis therapy at birth with Infasurf is indicated for premature infants <29 weeks of gestational age at significant risk for RDS. Infasurf prophylaxis should be administered as soon as possible, preferably within 30 minutes after birth.

Treatment

Infasurf therapy is indicated for infants ≤72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

WARNINGS

Infasurf is intended for intratracheal use only.

THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING INFASURF, OFTEN RAPIDLY IMPROVES OXYGENATION AND LUNG COMPLIANCE. Following administration of Infasurf, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.

Infasurf therapy is not a substitute for neonatal intensive care. Optimal care of premature infants at risk for RDS and new born infants with RDS who need endotracheal intubation requires an acute care unit organized, staffed, equipped, and experienced with intubation, ventilator management, and general care of these patients.

TRANSIENT EPISODES OF REFLUX OF INFASURF INTO THE ENDOTRACHEAL TUBE, CYANOSIS, BRADYCARDIA, OR AIRWAY OBSTRUCTION HAVE OCCURRED DURING THE DOSING PROCEDURES. These events require stopping Infasurf administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing can proceed with appropriate monitoring.

PRECAUTIONS

When repeat dosing was given at fixed 12-hour intervals in the Infasurf vs. Exosurf Neonatal® trials, transient episodes of cyanosis, bradycardia, reflux of surfactant into the endotracheal tube, and airway obstruction were observed more frequently among infants in the Infasurf-treated group.

An increased proportion of patients with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was observed in Infasurf-treated infants in the Infasurf-Exosurf Neonatal® controlled trials. These observations were not associated with increased mortality.

No data are available on the use of Infasurf in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation.

Data from controlled trials on the efficacy of Infasurf are limited to doses of approximately 100 mg phospholipid/kg body weight and up to a total of 4 doses.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis studies and animal reproduction studies have not been performed with Infasurf. A single mutagenicity study (Ames assay) was negative.

ADVERSE REACTIONS

The most common adverse reactions associated with Infasurf dosing procedures in the controlled trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). These events were generally transient and not associated with serious complications or death.

The incidence of common complications of prematurity and RDS in the four controlled Infasurf trials are presented in Table 3. Prophylaxis and treatment study results for each surfactant are combined.

Table 3 - Common Complications of Prematurity and RDS in Controlled Trials

Complication	Infasurf (N=1001) %	Exosurf Neonatal® (N=978) %	Infasurf (N=553) %	Survanta® (N=566) %
Apnea	61	61	76	76
Patent ductus arteriosus	47	48	45	48
Intracranial hemorrhage	29	31	36	36
Severe intracranial hemorrhage[a]	12	10	9	7
IVH and PVL [b]	7	3	5	5
Sepsis	20	22	28	27
Pulmonary air leaks	12	22	15	15
Pulmonary interstitial emphysema	7	17	10	10
Pulmonary hemorrhage	7	7	7	6
Necrotizing enterocolitis	5	5	17	18

[a] Grade III and IV by the method of Papile.
[b] Patients with both intraventricular hemorrhage and periventricular leukomalacia.

Follow-up Evaluations

Two-year follow-up data of neurodevelopmental outcomes in 415 infants enrolled in 5 centers that participated in the Infasurf vs. Exosurf Neonatal® controlled trials demonstrated significant developmental delays in equal percentages of Infasurf and Exosurf Neonatal® patients.

OVERDOSAGE

There have been no reports of overdosage with Infasurf. While there are no known adverse effects of excess lung surfactant, overdosage would result in overloading the lungs with an isotonic solution. Ventilation should be supported until clearance of the liquid is accomplished.

DOSAGE AND ADMINISTRATION

FOR INTRATRACHEAL ADMINISTRATION ONLY

Infasurf should be administered under the supervision of clinicians experienced in the acute care of newborn infants with respiratory failure who require intubation. Rapid and substantial increases in blood oxygenation and improved lung compliance often follow Infasurf instillation. Close clinical monitoring and surveillance following administration may be needed to adjust oxygen therapy and ventilator pressures appropriately.

Dosage

Each dose of Infasurf is 3 mL/kg body weight at birth. Infasurf has been administered every 12 hours for a total of up to 3 doses.

Directions for Use

Infasurf is a suspension which settles during storage. Gentle swirling or agitation of the vial is often necessary for redispersion. DO NOT SHAKE. Visible flecks in the suspension and foaming at the surface are normal for Infasurf. Infasurf should be stored at refrigerated temperature 2° to 8°C (36° to 46°F). THE 3mL VIAL MUST BE STORED UPRIGHT. Date and time need to be recorded on the carton when Infasurf is removed from the refrigerator. Warming of Infasurf before administration is not necessary.

Unopened, unused vials of Infasurf that have warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Infasurf should not be removed from the refrigerator for more than 24 hours. **Infasurf should not be returned to the refrigerator more than once.** Repeated warming to room temperature should be avoided. Each single-use vial should be entered only once and the vial with any unused material should be discarded after the initial entry.

INFASURF DOES NOT REQUIRE RECONSTITUTION. DO NOT DILUTE OR SONICATE.

Dosing Procedures

General

Infasurf should only be administered intratracheally through an endotracheal tube. The dose of Infasurf is 3 mL/kg birth weight. The dose is drawn into a syringe from the single-use vial using a 20-gauge or larger needle with care taken to avoid excessive foaming. Administration is made by instillation of the Infasurf suspension into the endotracheal tube.

Administration for Treatment of RDS

When used to treat RDS, Infasurf may be administered using either of the following 2 methods:

Exosurf Active Control Trials: Initial and Repeat Dosing

In the Infasurf vs. Exosurf® trials, Infasurf was administered intratracheally through a side-port adapter into the endotracheal tube. Two attendants, one to instill the Infasurf, the other to monitor the patient and assist in positioning, facilitated the dosing. The dose (3 mL/kg) was administered in two aliquots of 1.5 mL/kg each. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Administration was made while ventilation was continued over 20-30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning separated the two aliquots. Repeat doses of 3 mL/kg of birth weight, up to a total of 3 doses 12 hours apart, were given if the patient was still intubated.

Survanta Active Control Trials: Initial and Repeat Dosing

In the Infasurf vs. Survanta® trials, Infasurf was administered through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a $P_aO_2 \leq 80$ torr.

Administration for Prophylaxis of RDS at Birth

Dosing procedures are described under Administration for Treatment of RDS. The amount of a prophylaxis dose of Infasurf should be based on the infant's birth weight. Administration of Infasurf for prophylaxis should be given as soon as possible after birth. Usually the immediate care and stabilization of the premature infant born with hypoxemia and/or bradycardia should precede Infasurf prophylaxis.

Dosing Precautions

During administration of Infasurf liquid suspension into the airway, infants often experience bradycardia, reflux of Infasurf into the endotracheal tube, airway obstruction, cyanosis, dislodgement of the endotracheal tube, or hypoventilation. If any of these events occur, the administration should be interrupted and the infant's condition should be stabilized using appropriate interventions before the administration of Infasurf is resumed. Endotracheal suctioning or reintubation is sometimes needed when there are signs of airway obstruction during the administration of the surfactant.

HOW SUPPLIED

Infasurf (calfactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered glass vials containing 3 mL (NDC 61938-456-03) and 6 mL (NDC 61938-456-06) off-white suspension.

Store Infasurf (calfactant) Intratracheal Suspension at refrigerated temperature 2° to 8°C (36° to 46°F) and protect from light. **THE 3 mL VIAL MUST BE STORED UPRIGHT.** Vials are for single use only. After opening, discard unused drug.

Rx only

Manufactured by:
ONY Biotech Inc.
Amherst, NY 14228

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