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Upcoming Medical Meetings

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Neonatal Nurse Practitioners Symposium: Clinical Update and Review

Oct. 16-20, 2012; Clear Water Beach, FL USA
www.fannp.org/pages/conference.html

Third Port Said Neonatology Conference

Oct. 18-20, 2012; Port Said, Egypt
www.portsaidneogrp.com/index.html

Miami Neonatology 2012 - 36th Annual International Conference

Oct. 31-Nov. 3, 2012; Miami Beach, FL USA
pediatrics.med.miami.edu/neonatology/international-neonatal-conference

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The First Synthetic, Peptide-Containing Surfactant Approved in the United States for the Prevention of Respiratory Distress Syndrome (RDS) in Premature Infants

By Thomas H. Shaffer, MSE, PhD

Background

The fundamental principles associated with surface tension in the lungs were identified by Kurt Von Neergaard¹ in 1929. After a number of years and the collective efforts of many investigators, John Clements advanced the study of surface tension in the lungs by utilizing more definitive measures of surface tension and surface area. Clements² decided to explore the reason why premature infants who died of respiratory distress never had “foam” in lung washings, an observation reported in previous studies of normal lungs. It was not until 1959, however, that Avery and Mead³ published that “low surface tension in the lungs permits stability of the alveoli at end expiration...in lung extracts of immature infants dying with hyaline membrane disease, surface tension is higher than expected. This deficiency of surface active material may be significant in the pathogenesis of hyaline membrane disease.”

Subsequent research involved the characterization of the surface lining (surfactant) materials in the lung in efforts to develop a therapeutic intervention exogenous “surfactant replacement therapy” (SRT) “for infants who were born with surfactant deficiency.” During this new chapter of exploration, many laboratories studied the impact of natural surfactants derived from animals. As a result, the majority of SRTs presently on the market are derived from animal sources, which con-

tain low levels of surfactant protein (SP-B) relative to human surfactant, and the concentration of this protein can vary between lots of the same brand. Moreover, animal-derived surfactants contain foreign proteins that are potentially immunogenic. To date, current SRTs are labeled to be administered intratracheally, requiring mechanical ventilation. In contrast to animal-derived surfactant development, other investigators explored

“Because synthetic surfactants offer very advantageous scientific and clinical opportunities for improved neonatal care, they provide a gateway for the development of additional therapeutic interventions for neonatal care that have been unavailable with natural animal-derived surfactants....”

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References: 1. Rubin LP, et al. *Journal of Perinatology* advance online publication, 14 July 2011; doi:10.1038/jp2011.87. 2. Kanako IN, et al. *Arterioscler Thromb Vasc Biol.* 2007;27:2555-2562. 3. Canfield LM, et al. *Eur J Nutr.* 2003;42:133-141. 4. Schweigert FJ, et al. *Eur J Nutr.* 2004;43:39-44. 5. Patton S, et al. *Lipids.* 1990;25:159-165. 6. Jewell VC, et al. *Proc Nutr Soc.* 2001;60:171-178. 7. Connor SL, et al. *FASEB.* 2008;22:451-454.

NEW



The first synthetic, peptide-containing surfactant approved in the United States for the prevention of respiratory distress syndrome (RDS) in premature infants. ~ Shaffer, Thomas H.



DiscoveryLabs
Inspired Innovation

Figure 1: Schematic of the molecular structure of KL4-peptide. (courtesy of DiscoveryLabs).

the use of synthetic surfactants in an effort to: control formulation consistency and stability; reduce possible inflammatory responses to animal-derived materials in the human lung; and improve production and product availability.

Most notable in the area of synthetic SRT research is the arduous work of Charles Cochrane⁴ in collaboration with T. Allen Merritt. They are credited with the invention of synthetic KL₄ peptide and the subsequent drug, "lucinactant", the novel peptide synthetic surfactant (Figure 1). This formulation consists of phospholipids, a fatty acid, and sinapultide (KL₄ peptide), a 21-amino acid peptide that mimics the surface tension-lowering activity of human pulmonary surfactant protein B (SP-B), the most essential of the surfactant proteins for lung function. Lucinactant (Surfaxin[®], Discovery Laboratories, Inc.; Warrington, PA) has been recently approved by the US FDA for the prevention of Respiratory Distress Syndrome (RDS) in preterm infants at high risk for RDS.

Because synthetic surfactants offer very advantageous scientific and clinical opportunities for improved neonatal care, they provide a gateway for the development of additional therapeutic interventions for neonatal care that have been unavailable with natural animal-derived surfactants, as delineated below.

Preclinical Studies of Lucinactant

Numerous preclinical pharmacology studies have demonstrated that lucinactant has significant pharmacologic activity in mechanisms involving pulmonary surface tension-lowering ability and improving lung function and oxygenation comparable to other commercially available pulmonary surfactants. In addition, lucinactant has been shown *in vitro* to be resistant to inactivation by plasma proteins and oxidants when compared with other surfactants, to possess antimicrobial activity, and appears to modulate the pulmonary inflammatory response *in vitro*, as well as in animal studies.⁵⁻⁸ Furthermore, studies in a number of *in vivo* models have shown that combining the appropriate method of administration concurrent with lucinactant therapy potentiated the beneficial activity of lucinactant for the prevention and treatment of Respiratory Distress Syndrome (RDS).⁹ Finally, toxicology studies with lucinactant in numerous species revealed no notable systemic effects, and a study in guinea pigs provided no evidence of an immune reaction to the KL₄ peptide.

Overview of Clinical Studies with Lucinactant

Lucinactant was vigorously studied in numerous patient populations as part of a comprehensive clinical development program. Phase II pro-

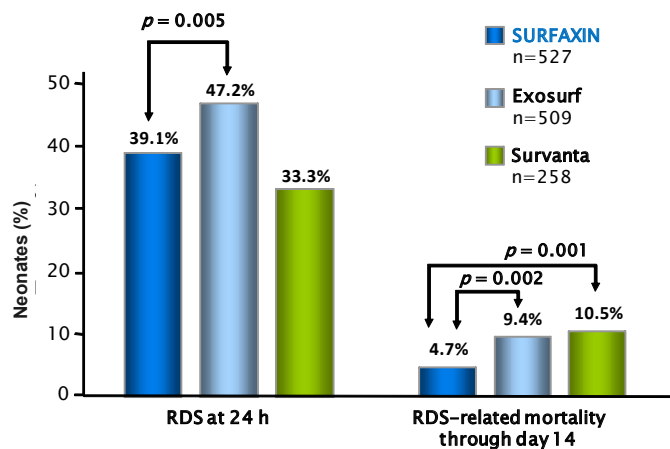


Figure 2. Incidence of RDS and RDS-Related Mortality in Premature Infants (600-1250g).

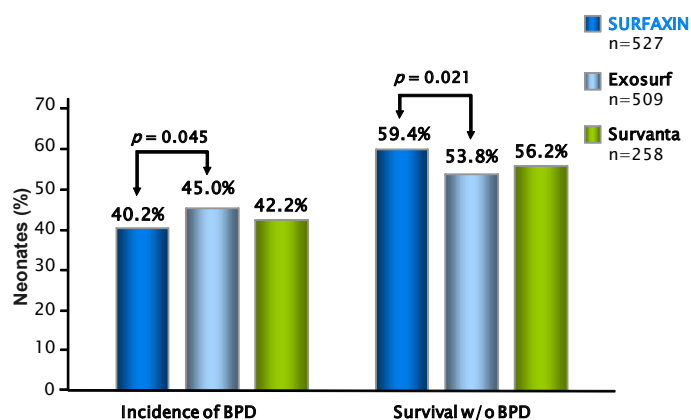


Figure 3. Incidence of BPD and Survival w/o BPD at 36 Weeks in Premature Infants (600-1250g).

grams were conducted in full-term infants with Meconium Aspiration Syndrome (MAS); very low birth weight (VLBW); premature infants at risk for bronchopulmonary dysplasia (BPD); premature infants at risk for RDS; children up to 2 years of age with acute hypoxemic respiratory failure (AHRF); adult subjects with mild persistent asthma (receiving aerosolized lucinactant); adult subjects with cystic fibrosis (receiving aerosolized lucinactant); and adult subjects with acute RDS (ARDS). In all of these studies, lucinactant appeared to be generally safe and well-tolerated, with a safety profile similar to other SRTs and/or standard of care treatment.

The primary focus of the lucinactant RDS clinical development program was to demonstrate that the formulation, administered via intratracheal instillation, was safe and effective in preventing RDS in preterm infants at risk for RDS. To support this indication, two Phase III trials were conducted in preterm infants: the pivotal study, SELECT, comparing lucinactant with colfosceril palmitate (Exosurf[®]) with beractant (Survanta[®]) serving as a reference arm, and the supportive Phase III study, STAR, to demonstrate non-inferiority of lucinactant with poractant alfa (Curosurf[®]).^{10,11} In both studies, premature infants were followed short-term (36 weeks PMA) and through one-year corrected age.¹²

In the SELECT study, lucinactant was shown to be significantly more effective than colfosceril palmitate in the primary outcomes of preventing RDS at 24 hours and reducing RDS-related mortality through 14 days.¹⁰ It also significantly lowered RDS-related mortality when compared with

Survanta ($p=0.001$) [Figure 2]. In addition, lucinactant had a beneficial effect on key secondary outcomes by significantly reducing the incidence of BPD (defined as requiring supplemental oxygen at 36 weeks PMA) and increasing survival without BPD at 36 weeks PMA compared with colfosceril palmitate (Figure 3).

In the STAR study, lucinactant was shown to be non-inferior to poractant alfa in the primary outcome of survival without BPD at Day 28 of life and was also associated with improved long-term survival compared with poractant alfa.^{11, 12}

In a combined analysis, data from the SELECT and STAR trials were pooled to evaluate the effect of the synthetically-derived lucinactant compared with the animal-derived surfactants beractant and poractant alfa on all-cause mortality over the short-term (28 days and 36 weeks PMA) and through one year corrected age.¹⁰⁻¹² In the pooled analysis, both short- and long-term mortality were significantly reduced in premature infants treated with lucinactant compared with those treated with the

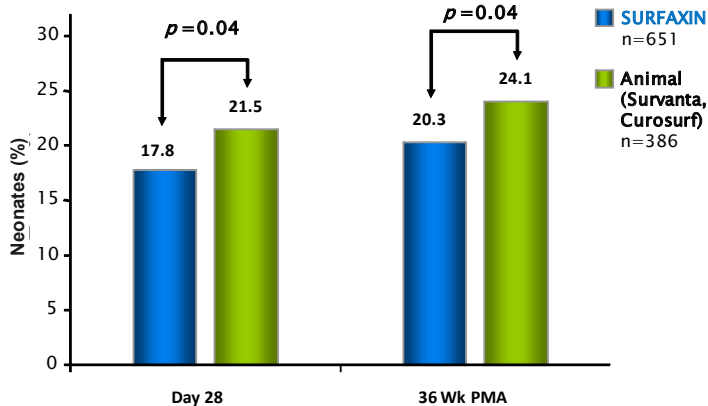


Figure 4. Incidence of Short-term (28-day and 36 Weeks PMA), All-cause Mortality in Premature Infants (600-1250g).

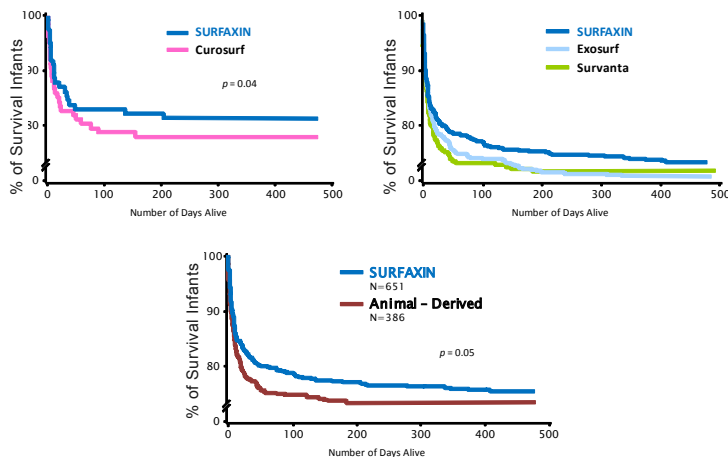


Figure 5. Incidence of Long-term (through 1 year corrected age), All-cause Mortality in Premature Infants (600-1250g).

animal-derived surfactants (Figure 4 and 5).

Reintubation after successful extubation, a noteworthy event related to significant morbidity and mortality, was an important outcome measure in both the SELECT and STAR studies. In a recently published post hoc analysis of reintubation rates, infants treated with lucinactant were ob-

served to have a lower rate of reintubation when compared with beractant (35% vs. 43%, respectively; $p=0.021$) and poractant alfa (33% vs. 47%, respectively; $p=0.021$).¹³

In the SELECT and STAR studies, lucinactant was considered safe and well-tolerated through the short-term and one-year corrected age follow-up. The safety profile of lucinactant in terms of complications of prematurity was comparable to that of colfosceril, beractant, and poractant alfa. Additionally, when data from the SELECT and STAR studies were pooled to further evaluate safety, no differences in the incidences of major complications of prematurity were detected with lucinactant when compared with animal-derived surfactants, beractant and poractant alfa

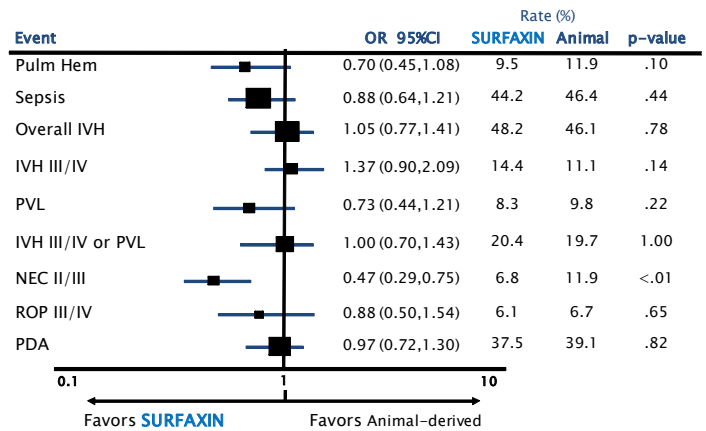


Figure 6. Incidences of Major Complications of Prematurity: Surfadoxin vs. Animal-Derived Surfactants (Survanta and Curosurf).

(Figure 6).

Typical, transient peri-dosing events were observed at higher rates with lucinactant versus the comparator surfactants in the SELECT and STAR studies, likely related to the volume of administration. It is important to note that the peri-dosing events observed in these studies did not appear to meaningfully impact short- or long-term clinical outcomes.

Lucinactant: the Gateway to Future Neonatal Therapies

The recent increased use of nasal CPAP (nCPAP) for the treatment of neonatal RDS has been popularized by the desire to avoid the invasiveness of endotracheal intubation and mechanical ventilation in preterm infants, as well as the success of this modality reported in studies as far back as the early 1970s.¹⁴ An analysis performed by Avery, et al, revealed that less aggressive ventilatory management (early nCPAP) at Columbia University led to lower rates of chronic lung disease (CLD) or BP.¹⁵ Retrospective cohort analyses have shown that nCPAP alone decreased the need for invasive treatment and the duration of respiratory support among preterm newborns with RDS when compared to those treated with intermittent mechanical ventilation (IMV).^{16, 17}

Nevertheless, a significant detriment to nCPAP therapy without endotracheal (ET) intubation is that it precludes the use of surfactant replacement therapy (SRT) for RDS prophylaxis and treatment, which has been established as standard of care and shown to be highly effective in reducing morbidity and mortality in preterm infants over the last two decades.¹⁸ Additionally, in a recent multicenter, randomized clinical study (COIN), significant nCPAP failure rates were observed with use of early nCPAP, and the delay or avoidance of SRT led to increased risk for pneumothorax.¹⁹ A series of clinical studies have prospectively examined the use of nCPAP followed by SRT, a technique known as InSurE (intubation, surfactant instillation, and extuba-

tion to nCPAP).²⁰⁻²² In general, these studies suggest that the InSurE approach appears to be safe and effective in decreasing subsequent nCPAP failure and intubation rates, air leakage, and length of mechanical ventilation, as well as subsequent dosing of surfactants.¹⁹⁻²² Despite the positive findings associated with InSurE, this approach still requires ET intubation, which may be a traumatic procedure and can be associated with adverse physiologic effects including bradycardia, fluctuations in blood pressure, hypoxia and increased intracranial pressure (ICP).^{22, 23} Additionally, repeated intubations with malposition of the ET tube during placement,²⁴ as well as rare iatrogenic tracheobronchial perforations reported with intubation, clearly indicate that ET intubation can result in serious adverse effects in neonates.^{25, 26}

Thus, attempts to avoid intubation in the treatment of RDS have led clinicians to administer surfactant in a direct non-invasive approach by using an aerosolized form of the drug. Several proof-of-concept clinical studies using aerosolized surfactants combined with nCPAP for prevention of RDS have been performed, demonstrating safety²⁷⁻²⁹ and, in one study, a significant response to treatment.²⁸ All of the studies utilized a late treatment schedule of surfactant delivery from 2 to 9 hours of life.

The potential benefits of delivering aerosolized surfactants without the requirements for ET intubation are clearly appealing. Optimization of a surfactant formulation that: (i) can be effectively aerosolized without degradation or loss of activity; (ii) is resistant to inactivation; and (iii) possesses anti-inflammatory activity²⁹ could provide additional benefits in improving outcomes of preterm infants that require SRT to prevent or treat RDS.

Lucinactant (KL₄ surfactant) has been shown to possess all the above attributes. Lucinactant has been shown *in vitro* to be more resistant to inactivation by inflammatory mediators such as fibrinogen, C-reactive protein, and platelet activating factor compared to beractant,³⁰ and significantly decreased hyperoxia-induced interleukin (IL)-6 and -8 secretions from human airway epithelium.⁸ An *in vivo* study on an LPS-induced lung injury model treated with hyperoxia and lucinactant showed decreased lung edema, leukocyte influx into the alveoli, and blockade of polymorphonuclear leukocyte (PMN) infiltration when compared to untreated controls and beractant.³¹ In the preterm lamb model of RDS, lucinactant-treated animals were observed to have significantly lower levels of IL-6, IL-8 and myeloperoxidase (MPO) in the lung homogenate and IL-6 and 8 plasma concentrations compared to poractant alfa or beractant.³² The intrinsic properties of lucinactant to modulate the pulmonary inflammatory response may be of particular importance in preventing BPD. Data from a recent multicenter clinical study suggested that risk for BPD and death was associated with higher concentrations of IL 1 β , 6, 8 and 10, interferon γ , and lower concentrations of IL-17.³³

The benefits of nCPAP and the unique attributes of lucinactant – namely, the development of aerosolized lucinactant delivered non-invasively with nCPAP for prevention of RDS, with the potential for improving survival without BPD and reducing the incidences of nCPAP failure, air leak and BPD – provides a solution for an important unmet medical need.

Aerosolized Lucinactant

Initially aerosol studies focused on testing “off-the-shelf,” commercially available aerosol generators to deliver lucinactant. Based upon the

bench evaluation of these devices and subsequent testing of one of these devices (a vibrating membrane nebulizer: Aeroneb-Pro®, Aerogen, Dangan, Galway, Ireland) in the first aerosol lucinactant proof-of-concept study in humans, it became apparent that this device was suboptimal for delivering viscous materials such as lucinactant. Extensive engineering efforts were refocused on developing an alternate aerosol generator capable of delivering highly concentrated aerosolized surfactant to patients in order to provide sufficient amounts of active drug for an efficacious response within a relatively short period of time. These efforts led to the identification and subsequent development and optimization of a novel aerosol generation technology, the capillary aerosol generator (CAG) by DiscoveryLabs.

During the optimization of the CAG, characterization of pre- and post-aerosolization of the drug showed that aerosolized lucinactant retained both its chemical composition and surface tension-lowering properties. As shown below (Figure 7), the surface tension of aerosolized lucinactant measured by pulsating bubble surfactometry (PBS) suggests that aerosolization does not significantly alter the physical properties of the drug product.

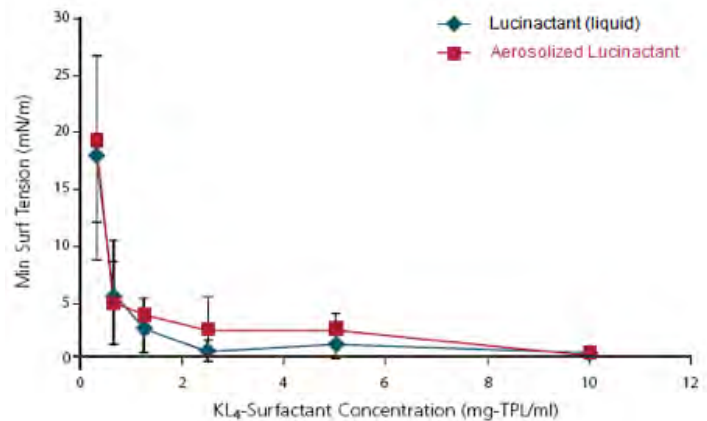


Figure 7. Dilution curve on PBS pre and post-aerosolization.

An *in vivo* fetal rabbit biological activity test demonstrated improvement in respiratory system compliance at 30 minutes after intratracheal instillation of lucinactant collected post-aerosolization, which was similar to compliance obtained after instillation of control liquid formulation of lucinactant.

In studies conducted to compare the output rates of the CAG with commercially available aerosol generators, utilizing both saline (as a low viscosity control) and lucinactant, CAG aerosol output rates were consistently greater for all test articles³⁴ (Figure 8).

The CAG drug/device delivery system consists of a base unit and a single use disposable delivery system that includes a disposable aerosol generator (CAG), a disposable, proprietary nCPAP connector, a dispos-

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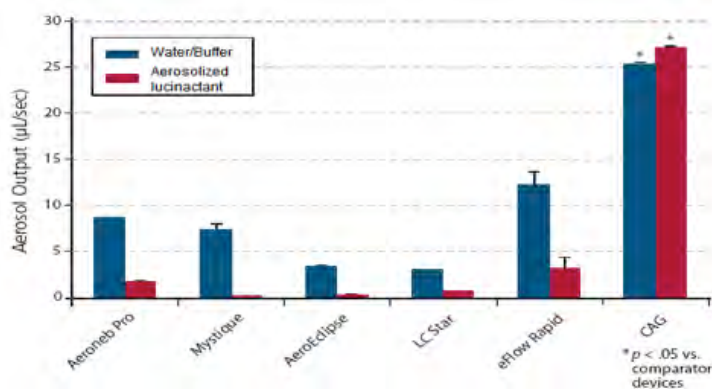


Figure 8. Aerosol output rates for saline and lucinactant generated with different aerosol generators.

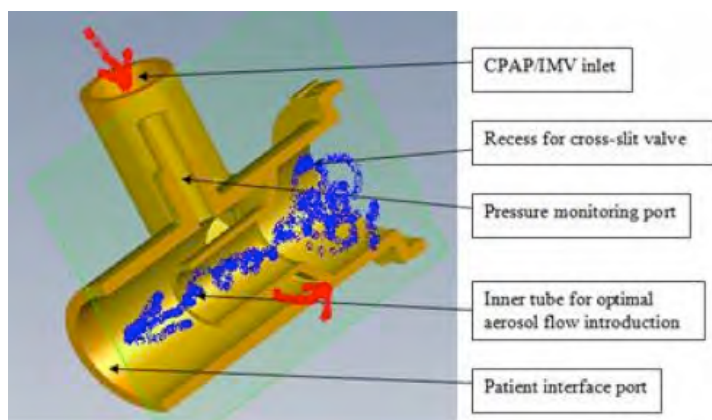


Figure 9. Schematic of the Afectair® (ventilation/nCPAP) connector.

able fluid trap assembly, a drain bottle assembly, a drug reservoir filter assembly and a disposable drug reservoir.

Aerosol Delivery System : Ventilation/nCPAP Connector

Aerosolized drugs have been used routinely in the NICU for several decades; however, the results of clinical studies have been generally disappointing.³⁴⁻³⁶ It is probable that the aerosol systems used in these studies were not optimal for drug delivery to the lungs.

DiscoveryLabs has designed a novel aerosol delivery system (i.e., ventilation/nCPAP connector) that allows for efficient aerosol entrainment into the patient interface during nCPAP treatment (Figure 9). This ventilation/nCPAP connector, while not increasing dead space volume, directs the aerosol towards the patient, thereby assuring that potential dilution of the ventilator gas flow is prevented. Both an in vitro dilution study and a resistance study demonstrated technical advantages of this novel aerosol delivery system.

Preclinical Drug/Aerosol Device Experience

The drug/device combination consisting of lucinactant and the current CAG device (including the Afectair® connector) has been evaluated in a preclinical study using the well-established preterm lamb RDS model. The objective of this study was to assess the safety and effectiveness of aerosolized lucinactant on lung mechanics, histomorphology and biomarkers of lung inflammation in spontaneously breathing, nCPAP-supported preterm lambs. The study results, presented at several scientific congresses, showed that relative to treatment with nCPAP alone, aerosolized lucinactant delivery by CAG technology improved pulmonary mechanics, lung structure integrity, and reduced lung inflammation in very preterm lambs. These observations support the potential utility of this novel approach to treat preterm infants with respiratory distress syndrome.³⁷ The study is expected to be published within the next year.

Clinical Experience with Aerosolized Lucinactant

Although there have not been extensive clinical studies with aerosolized lucinactant, a pilot study³⁸ was conducted to determine the feasibility and safety of prophylactic aerosolization of lucinactant delivered by nCPAP to preterm infants at risk for RDS. This study was conducted prior to the development of the aforementioned CAG, and an FDA approved aerosol generator (Aeroneb-Pro® vibrating membrane nebulizer, Aerogen Ltd., Dangan, Galway, Ireland) was used to aerosolize lucinactant.

Infants were stratified by gestational age (GA) and enrolled into either treatment Group 1 (aerosolized lucinactant re-treatment separated by at

least three hours) or treatment Group 2 (aerosolized lucinactant re-treatment separated by at least one hour). A total phospholipid (TPL) concentration of 20 mg/mL of lucinactant was used in the Aeroneb-Pro. The predetermined Aeroneb-Pro output rate of Aerosurf was 4 µL/sec and the inhaled dose, based on bench testing with a lung simulator, was 0.4 mg TPL per minute.³⁹ Thus, over a three-hour period, the maximal potential inhaled dose of Aerosurf delivered to the infant was approximately 72 mg TPL. Mass median aerodynamic diameter (MMAD) of the aerosol generated by the system was previously established at $1.9 \pm 0.3 \mu\text{m}$.³⁹ All neonates received the initial three-hour treatment within 30 minutes of birth, and three re-treatments were permitted within 48 hours based upon clinical response.

Seventeen infants were enrolled (birth weights 1033-2870 g); 11 in the 30-32 weeks GA stratum, and six in the 28-29 weeks GA stratum. All infants survived: five of 17 (29.4%) required subsequent ETT surfactant replacement therapy (SRT); four of 17 (23.5%) were diagnosed with RDS at 24 hours; and two of 17 (11.8%) were diagnosed with BPD at 28 days of life. Although the number of subjects is small, the aerosol nCPAP failure rates, RDS rates, and the BPD rates are lower than those reported in the current literature. Mean FiO_2 was 0.4 at baseline and 0.32 at four hours post treatment. Aerosolized lucinactant was well tolerated with transient desaturations observed during dosing without bradycardia or hypotension. Variability in output rates of the Aeroneb-Pro was observed, leading to different average dispensed drug volumes per treatment per patient.

Lyophilized Form of Lucinactant

Past clinical experience provides ample evidence that liquid instillate lucinactant is efficacious and well-tolerated in premature infants at risk for RDS. As described above, liquid lucinactant significantly decreased the incidence of RDS and RDS-related mortality, decreased the incidence of BPD, and increased the rate of survival without BPD. Moreover, short- and long-term mortality was significantly reduced with lucinactant versus the animal-derived surfactants. In the clinical studies conducted in premature infants at risk for RDS, lucinactant appeared to be generally safe and well-tolerated.

Based on the favorable material characteristics and potential technical / logistical advantages of the lyophilized dosage form of lucinactant, initial lung compliance findings related to Surfaxin LSTM in a pre-term lamb study, and extensive clinical experience with liquid lucinactant, it is reasonable to expect that the efficacy and safety profiles of lyophilized lucinactant in premature infants with RDS would be comparable to that of the liquid dosage form, but with potentially easier preparation. Thus, the (Continued on Page 9)

For the 92% of neonatologists who expressed concerns over exposing newborn infants to animal-derived medications¹...

Discovery Labs heard you

Dear Healthcare Provider,

Above most, you understand the potential challenges that lie ahead for an infant that is born prematurely. Your goal is to ensure each infant has the quality of life her parents long for and which she deserves. You also know that not all medications are created equal. That is why, according to a recent publication in the *Journal of Neonatal-Perinatal Medicine*; nearly all neonatologists interviewed stated they were concerned about the exposure of newborn infants to animal-derived medications.¹

In March, the US FDA approved the first and only synthetic peptide-containing surfactant, SURFAXIN® (lucinactant). Approved for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS, SURFAXIN is the first new alternative to animal-derived surfactants to be approved by the FDA in more than two decades. Importantly, the safety and efficacy of SURFAXIN was evaluated in two phase 3 clinical trials^{2,3}, which included direct comparisons to the animal-derived surfactants, Survanta® and Curosurf®. SURFAXIN will become available as a commercial product later this year.

The approval of SURFAXIN represents more than just a therapeutic alternative for neonatologists and NICU parents. It is the embodiment of the unwavering commitment Discovery Labs has to the respiratory critical care community today and tomorrow. We have persisted because of our belief in the series of new solutions that we are developing to improve patient lives and the standard of respiratory critical care.

As you contemplate the best treatment options for your neonatal patients, we would be happy to provide you with more information about SURFAXIN and explore ways to work together to alleviate the concerns of neonatologists and NICU parents who have waited for more than a decade for a new and effective alternative for the prevention of RDS in preterm infants.

Together, we can reach our goal of redefining RDS management and give preterm infants the life they deserve.

Sincerely,



Dr. Thomas F. Miller
Chief Operating Officer
Discovery Laboratories, Inc.
Warrington, PA



IMPORTANT SAFETY INFORMATION

SURFAXIN (lucinactant intratracheal suspension) is intended for intratracheal use only. The administration of exogenous surfactants, including SURFAXIN, can rapidly affect oxygenation and lung compliance. SURFAXIN should be administered only by clinicians trained and experienced with intubation, ventilator management, and general care of premature infants in a highly supervised clinical setting. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Most common adverse reactions associated with the use of SURFAXIN are endotracheal tube reflux, pallor, endotracheal tube obstruction, and need for dose interruption. During SURFAXIN administration, if bradycardia, oxygen desaturation, endotracheal tube reflux, or airway obstruction occurs, administration should be interrupted and the infant's clinical condition assessed and stabilized. SURFAXIN is not indicated for use in acute respiratory distress syndrome (ARDS).

Please see accompanying brief prescribing information or visit www.surfaxin.com for full prescribing information.

¹ S. Sarkar and S.M. Donn, *Journal of Neonatal-- Perinatal Medicine* 4 (2011) 235-239

² F. R. Moya, et al; *Pediatrics* 2005;115;1018-- - 1029

³ S. K. Sinha, et al; *Pediatrics* 2005;115;1030-- - 1038

Surfaxin[®]

(Lucinactant)

Intratracheal Suspension

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full prescribing information.

INDICATIONS AND USAGE

SURFAXIN is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Acute Changes in Lung Compliance

Administration of exogenous surfactants, including SURFAXIN, can rapidly affect lung compliance and oxygenation. SURFAXIN should be administered only by clinicians trained and experienced in the resuscitation, intubation, stabilization, and ventilatory management of premature infants in a clinical setting with the capacity to care for critically ill neonates. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Administration-Related Adverse Reactions

Frequently occurring adverse reactions related to the administration of SURFAXIN include bradycardia, oxygen desaturation, reflux of drug into the endotracheal tube (ETT), and airway/ETT obstruction.

Increased Serious Adverse Reactions in Adults with Acute Respiratory Distress Syndrome (ARDS)

Adults with ARDS who received lucinactant via segmental bronchoscopic lavage had an increased incidence of death, multi-organ failure, sepsis, anoxic encephalopathy, renal failure, hypoxia, pneumothorax, hypotension, and pulmonary embolism. SURFAXIN is not indicated for use in ARDS.

Clinical Trials Experience

The efficacy and safety of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a single randomized, double-blind, multicenter, active-controlled, multi-dose study involving 1294 premature infants (Study 1). Infants weighed between 600 g and 1250 g at birth and were 32 weeks or less in gestational age. Infants were randomized to receive 1 of 3 surfactants, SURFAXIN (N = 524), colfosceril palmitate (N = 506), or beractant (N = 258). Co-primary endpoints were the incidence of RDS (defined as having a chest x-ray consistent with RDS and an $FiO_2 \geq 0.30$) at 24 hours and RDS-related mortality at 14 days. The primary comparison of interest was between SURFAXIN and colfosceril palmitate with the intent of demonstrating superiority. Beractant served as an additional active comparator. Compared to colfosceril palmitate, SURFAXIN demonstrated a statistically significant improvement in both RDS at 24 hours and RDS-related mortality through Day 14. A second multicenter, double-blind, active-controlled study involving 252 premature infants was also conducted to support the safety of SURFAXIN (Study 2). Infants weighed between 600 g and 1250 g and were less than 29 weeks in gestational age. Infants were randomized to receive 1 of 2 surfactants, SURFAXIN (N = 124) or poractant alfa (N = 128).

The safety data described below reflect exposure to SURFAXIN administered intratracheally to infants at a dose of 5.8 mL per kg (up to 4 doses) in either 4 aliquots (Study 1) or 2 aliquots (Study 2) in 643 premature infants.

Comparator surfactants colfosceril palmitate and beractant were administered at the recommended doses (5.0 and 4.0 mL per kg, respectively) while the first dose of poractant alfa administered (2.2 mL per kg) was less than the recommended dose of 2.5 mL per kg. Any subsequent doses of poractant alfa were at the recommended 1.25 mL per kg dose.

Overall, the incidence of administration-related adverse reactions was higher in infants who received SURFAXIN compared to other surfactants (Table 1) and resulted in a greater proportion of infants treated with SURFAXIN who experienced administration-related oxygen desaturation and bradycardia. For Study 1, oxygen desaturation was reported in 17%, 9%, and 13% and bradycardia for 5%, 2%, and 3% of infants treated with SURFAXIN, colfosceril palmitate, and beractant, respectively. For Study 2, oxygen desaturation was reported in 8% and 2% and bradycardia in 3% and 2% of infants treated with SURFAXIN and poractant alfa, respectively.

These adverse reactions did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants (Table 2).

Table 1. Administration-Related Adverse Reactions in SURFAXIN Controlled Clinical Studies^a

	Study 1 ^b			Study	
	SURFAXIN (N = 524)	Colfosceril palmitate (N = 506)	Beractant (N = 258)	SURFAXIN (N = 119)	Poractant alfa (N = 124)
Total Doses Administered	994	1038	444	174	160
Total Number of Events (Events per 100 Doses)					
ETT Reflux	183 (18)	161 (16)	67 (15)	47 (27)	31 (19)
Pallor	88 (9)	46 (4)	38 (9)	18 (10)	7 (4)
Dose Interruption	87 (9)	46 (4)	30 (7)	7 (4)	2 (1)
ETT Obstruction	55 (6)	21 (2)	19 (4)	27 (16)	1 (1)

^a Table includes only infants who received study treatment.

^b Study 1 doses were administered in 4 aliquots.

^c Study 2 doses were administered in 2 aliquots.

Table 2. Common Serious Complications Associated with Prematurity and RDS in SURFAXIN Controlled Clinical Studies Through 36-Weeks Post-Conceptual Age (PCA)

	Study 1			Study 2	
	SURFAXIN (N = 527) %	Colfosceril palmitate (N = 509) %	Beractant (N = 258) %	SURFAXIN (N = 119) %	Poractant alfa (N = 124) %
Apnea	52	52	46	66	75
Intraventricular hemorrhage, all grades	52	57	54	39	38
-Grade 3/4	19	18	21	13	8
Periventricular leukomalacia	10	10	12	4	9
Acquired sepsis	44	44	44	45	52
Patent ductus arteriosus	37	35	37	43	44
Retinopathy of prematurity, all grades	27	26	25	32	31
-Grade 3/4	6	7	6	5	9
Necrotizing enterocolitis, all grades	17	17	19	13	15
-Grade 2/3	6	8	14	8	8
Pulmonary air leak through Day 7, all types	15	17	14	9	7
-Pulmonary interstitial emphysema	9	10	10	3	5
-Pneumothorax	3	4	2	4	1
Pulmonary hemorrhage	10	12	14	6	9

All-cause mortality through 36-weeks PCA was similar regardless of which exogenous surfactant was administered.

Adverse reactions reported in the controlled clinical studies through 36-weeks PCA occurring in at least 10% of infants were anemia, jaundice, metabolic acidosis, oxygen desaturation, hyperglycemia, pneumonia, hyponatremia, hypotension, respiratory acidosis, and bradycardia. These reactions occurred at rates similar to the comparator surfactants.

No assessments for immunogenicity to SURFAXIN were performed in these clinical studies.

Follow-up Evaluations

Twelve-month corrected-age follow-up of 1546 infants enrolled in the 2 controlled clinical studies demonstrated no significant differences in mortality or gross neurologic findings between infants treated with SURFAXIN and those treated with the comparator surfactants (colfosceril palmitate, beractant, or poractant alfa).

OVERDOSAGE

There have been no reports of overdose following the administration of SURFAXIN.

HOW SUPPLIED/STORAGE AND HANDLING

SURFAXIN (lucinactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered, clear glass vials containing 8.5 mL of white suspension (NDC 68628-500-31). One vial per carton.

Store SURFAXIN in a refrigerator at 2° to 8°C (36° to 46°F) and protect from light until ready for use. Do not freeze. Vials are for single use only. Discard any unused portion of SURFAXIN. Discard warmed vials of SURFAXIN if not used within 2 hours of warming.



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lyophilized dosage form is another important step forward with respect to convenience of administration.

Conclusion

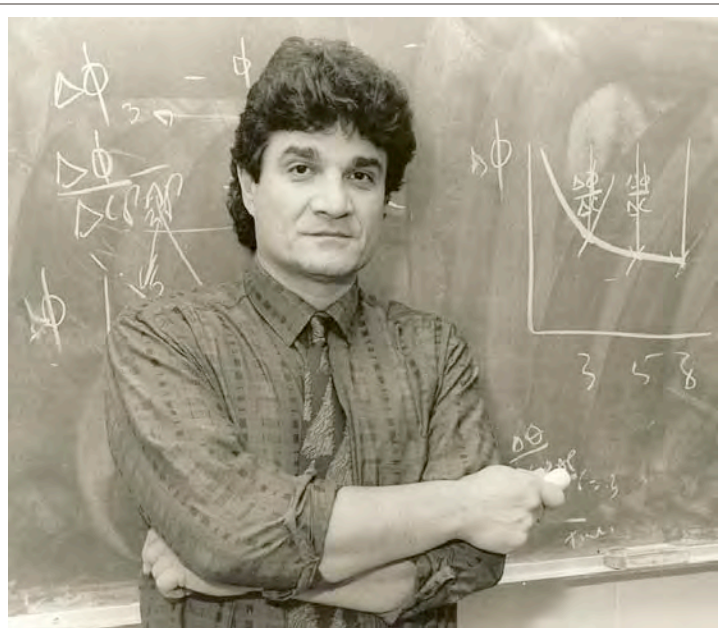
The "Bench to Bedside" story of the first synthetic, peptide-containing surfactant approved in the United States has been a journey involving over 30 years of research. Charles Cochrane and DiscoveryLabs should be proud of their great accomplishments in advancing the standard of care for pulmonary medicine. Of tantamount significance is that this therapy was initiated with a focus on premature infants at risk for RDS, a complication of prematurity that has resulted in many infant deaths. The discovery and approval of lucinactant serve as a gateway for the future development of lyophilized surfactant, the development of a new aerosolization technology that protects the therapeutic effectiveness of KL₄ surfactant, and a simple, but elegant solution in a ventilator/CPAP connector (Afectair®) for delivering these therapies to premature infants and neonates, our most vulnerable and fragile patient population.

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Thomas H. Shaffer, MS.E., PhD *Biography*

Dr. Shaffer has extensive experience as an active scientist in pulmonary research with special attention to the needs of the neonatal and pediatric populations. Dr. Shaffer's revolutionary work with perfluoro-carbon treatments for respiratory distress syndrome is known worldwide, and he is considered an international expert in this field. His group was the first to demonstrate that liquid ventilation could be performed in humans (*Lancet*, 1989). Over the years, his work has been cited and featured in the press, video media and film.

Since 1974, Professor Shaffer has been continuously supported by NIH grants (23), Office of Naval Research (3), academic, corporate and private institutional awards (53 total). His early NIH grants were awarded during a period when corporate sponsors were not readily supporting work in his area of interest, and the resultant science acted as a catalyst for procuring many other grants from the private and corporate sectors. In September, 2004, Dr. Shaffer was awarded a \$10.2 million Center for Biomedical Research Excellent (COBRE) grant from the National Institutes of Health for the development of a Center for Pediatric Research (CPR) at the Alfred I. duPont Hospital for Children in Wilmington, Delaware. In addition, as part of the ARRA program, he was awarded a \$1.6 million in supplements to this program for 2009-2010. On September 17, 2010, the Center for Pediatric Research (CPR) at the Nemours/Alfred I. duPont Hospital for Children was awarded an additional 5-year, \$9.5-million Center for Biomedical Research Excellence (COBRE) grant from the National Institutes of Health (NIH), National Center for Research Resources (NCRR). This competitive award will allow Nemours to continue to expand the CPR and support the recruitment of additional faculty to this diverse pediatric clinical and research facility. He serves as the Director of the new Center and administers its staff, revenues and research. Dr. Shaffer clearly understands translational research, having moved multiple intellectual properties from the bench top to the clinic and on to commercialization.

Dr. Shaffer's contribution to the literature has been significant. He has published 75 book chapters, 232 peer-reviewed manuscripts (with another 20 in review or in press), and 514 abstracts. His clinical manuscripts have been published in *Lancet*, *The New England Journal of Medicine*, *the Journal of Pediatrics*, *Pediatrics*, *Critical Care Medicine* and many more highly respected and well-read periodicals. In addition, he has published basic science manuscripts in the *Journal of Applied Physiology*, *the American Journal of Physiology*, and *the American Journal of Circulatory Research*. He serves on the Editorial Boards of three scientific journals and is a journal reviewer for another 22 publications.

In his faculty role at the University of Pennsylvania, Temple University School of Medicine and Thomas Jefferson School of Medicine, Dr. Shaffer has mentored 43 graduate students and 55 post-doctoral Fellows during the past 38 years. Many of these former students now hold faculty positions in prestigious medical schools at the University of Pennsylvania, Stanford University, Columbia University, the University of California at Davis, SUNY in Buffalo, New York, the Temple University School of Medicine, Bowman Gray, and the University of Washington.

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Global Neonatology Today Monthly Column - Millennium Development Goals: Where We Are in 2012?

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

As the U.N. Millennium Development Goals' (MDGs) target date of 2015 is fast approaching, the question arises: "What happens after 2015?" Many thoughts and plans are being floated around trying to answer that question.

As discussed in this column, The eight Millennium Development Goals declared in 2000 are the key areas to focus on in order to improve the overall well-being of people around the world. Simply stated, they include: poverty reduction, improvement in education, improvement in gender equality, infant and mortality reduction, sustaining environmental safety, and the creation of a global alliance to attain these goals through collective global effort.

During the last ten years, countries across the globe have been focusing their efforts to meet the targets by 2015. Some have succeeded, some are on track, still others have yet to show progress. Achieving the MDGs requires a great amount of planning within the country, as well as help from developed countries. It requires the support of governments, international organizations, civil society and businesses alike. Although there are great expectations that the target will be met by 2015, there are also doubts, given intervening global events, whether these expectations are realistic. The unforeseen economic crises leading to financial instabilities around the globe has pushed back the expected progress. However, it is the general opinion that MDGs have provided important directions for future work and have spurred dialogue among stakeholders at national and international levels. The emphasis on goals and targets has brought home global-thinking at the local levels. However, there is a criticism from some in that the Millennium Goals are too big and too diffuse to be successful. Both donor and recipient countries have experienced economic woes, regional conflicts and natural disasters that have impeded their progress. Nevertheless, there is a general feeling among policymakers and civil society that serious gains have been

made in the fight against poverty, hunger and disease. The following points highlight the gains made so far according to analysts:

1. Despite significant setbacks after the 2008-2009 economic crisis, the world is on track to reach the MDG poverty-reduction target by 2015.
2. Some of the world's poorest countries, including: Burundi, Rwanda, Samoa, Togo and the United Republic of Tanzania, have made the greatest strides in education.
3. Every region has made progress in improving access to clean drinking water.
4. Investments in preventing and treating HIV have caused new HIV infections to drop by 21% in 1997, when they peaked.
5. The number of deaths of children under the age of five declined from 12.4 million in 1990 to 8.1 million in 2009.
6. Also, maternal deaths have decreased significantly.

Now the question is: What happens after 2015?

Several ideas are floating around; they include: continuing the Goals for an extended period and/or initiating a new set of goals. These plans were discussed at the recent meeting *United Nations Conference on Sustainable Development (UNCSD)*, that took place in Rio or better known as "Rio+20." We will discuss that in the next issue.

The Clock is Ticking !!!

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