Lucinactant: New and Approved, But Is It an Improvement?

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In 1959, surfactant deficiency was identified as the cause of respiratory distress syndrome (RDS). Numerous surfactant replacement therapies were subsequently developed, including first-generation synthetic protein-free surfactants, animal-derived minced lung or lung lavage extracts, and human amniotic fluid extract. In the 1980s, randomized controlled trials assessing these therapies consistently demonstrated benefits including decreased mortality. During this time, the superiority of animal-derived products compared to first-generation synthetic products was reported, demonstrating the significant role of surfactant proteins.¹ The American Academy of Pediatrics' statement concerning surfactant replacement therapy for respiratory distress in neonates summarized the comparison by stating both animal-derived and first-generation synthetic surfactants are beneficial, but the use of animal-derived products resulted in lower mortality rates, lower oxygen and ventilation requirements, and fewer pneumothoraces.² Currently, first-generation protein-free synthetic surfactants have been removed from most markets.

The search for new and improved synthetic surfactants continues because of theoretical concerns of infectious and antigenic complications as well as drug shortages of animal-derived products, although in vitro and clinical trials do not support these concerns.² The agents currently being investigated are supplemented with peptides or proteins to mimic natural surfactant proteins. One such product, lucinactant (Surfaxin; Discovery Laboratories, Inc., Warrington, PA), was approved in March 2012 by the US Food and Drug Administration. Lucinactant contains two phospholipids and a high concentration of sinapultide (also known as KL-4), a synthetic peptide designed to have similar activity to sur-

factant protein B. Sinapultide is considered to be more resistant to inactivation by endogenous serum proteins and reactive oxygen species than naturally occurring surfactant protein B.^{3,4} The commercial preparation of lucinactant is available as a gel formulation in single-use vials of 8.5 mL. Prior to use, it requires warming for 15 minutes in a dry block heater preheated to 44°C. The vial is then shaken vigorously until it becomes a free-flowing suspension and is allowed to cool to body temperature. The approved dose is 5.8 mL/kg given intratracheally as frequently as every 6 hours for up to four doses in the first 48 hours of life.⁵

To date, two multicenter, double-blind, randomized, controlled clinical trials^{6,7} and a 1-year follow-up study⁸ of lucinactant have been published. The Surfaxin in Therapy Against RDS (STAR) trial compared lucinactant to poractant, an animal-derived surfactant, in a noninferiority trial with the primary outcome of survival to 28 days without bronchopulmonary dysplasia (BPD). The trial was stopped early due to slow enrollment after only approximately 50% of the estimated sample size could be reached, with no differences found between the two surfactant replacement therapies.⁶ The Safety and Effectiveness of Lucinactant versus Exosurf in a Clinical Trial (SELECT) compared lucinactant to colfosceril, a first-generation synthetic surfactant, and included beractant, an animal-derived surfactant as a reference agent in a 2:2:1 ratio. The primary outcomes were the development of RDS at 24 hours and RDS-related deaths by 14 days of life. Lucinactant significantly reduced the incidence of RDS compared with colfosceril and reduced RDS-related mortality through 14 days of life compared with both colfosceril and beractant.⁷ A 1-year follow-up study compared

survival, pulmonary, and neurodevelopmental outcomes of those infants who received lucinactant with those of infants who received other surfactants in the STAR trial and SELECT, individually and in a combined analysis. Subjects who were lost to follow-up or, if consent was withdrawn, were considered deaths with analyses repeated with raw data. When the infants in the two trials were compared separately and infants with missing data were counted as deaths, there were significantly more infants alive through 1 year corrected age who received lucinactant than those who received poractant ($p=0.04$), but no differences were found in the comparison among lucinactant, colfosceril, and beractant. In the combined analysis, when infants with missing data were counted as deaths, there was a lower mortality rate with lucinactant than with animal-derived surfactants ($p=0.05$), with no significant differences found by using raw data. There also were no significant differences in rehospitalizations, respiratory illnesses, or neurological follow-up assessments.⁸

Although the use of pulmonary surfactant for neonatal RDS has been accepted as a cost-effective medical therapy, information regarding pharmacoeconomic comparisons between individual products is limited. Lucinactant has been compared to the animal-derived surfactant beractant in a study published in this journal in 2006.⁹ In that study, data collected from SELECT were used to evaluate costs associated with the use of the two products in terms of medical resource use among study participants and were extrapolated to the population of all preterm very-low-birth weight (VLBW) infants treated with surfactant in the United States. Although pharmacy costs were \$461 higher in patients treated with lucinactant, the synthetic surfactant was found to save \$9264 in medical costs, yielding an overall healthcare savings of \$8803 per patient. When extrapolated to savings realized by treating more than 35,000 VLBW infants who received surfactant in the United States, the authors concluded that the US health care system could be spared over \$300 million dollars if those neonates were treated with lucinactant.⁹ However, in a cost minimization analysis published in this journal in 2004, poractant was found to save between 20% and 53% over beractant depending on which one of three cost models was being evaluated.¹⁰ It is possible that the cost savings with lucinactant compared

to poractant may not be as robust compared to beractant. How institutional costs will compare between lucinactant and other surfactants in the clinical setting is currently unknown and may be influenced by factors outside of the SELECT design, such as timing of administration, alternative patient populations being treated, use of prophylactic versus rescue therapy, number of doses administered, acquisition cost, product wastage, preparation time, and use of nasal continuous positive airway pressure (NCPAP). Furthermore, the effect of geographic distribution among participating centers in SELECT on surfactant use and ventilatory practices¹¹ may also play a role in the pharmacoeconomics of surfactant selection.

In this issue of *Journal of Pediatric Pharmacology and Therapeutics*, Guardia and colleagues provide a unique perspective with regard to the economic implications associated with reintubation rates in preterm infants treated with lucinactant compared to animal-derived surfactants in the SELECT and STAR trial.¹² As noted by the authors, extubation failure carries not only a significant risk of increased morbidity¹³ but also increased cost implications in a health care environment currently burdened with finding new and innovative ways to reduce expenditures. Their study reports relevant cost savings associated with decreased reintubation rates following the use of lucinactant in premature neonates weighing between 600 and 1250 grams who were intubated at birth due to their risk of developing RDS.¹² Although the use of lucinactant appears promising in this regard, factors other than surfactant selection play an important role in extubation success, including patient gestational age and birth weight, antenatal steroid use, concurrent illnesses, provider-specific criteria for reintubation, and the use of prophylactic methylxanthine therapy¹⁴ and early NCPAP.¹⁵⁻¹⁷ Patient demographics with regard to gestational age, birth weight, and antenatal steroid use were all well matched in both trials, so it is unlikely differences in these factors played a role in extubation success or failure. However, neither routine use of prophylactic methylxanthines nor early NCPAP had come into widespread clinical use at the time these trials were conducted, and both have been shown in subsequent clinical trials to reduce the need for mechanical ventilation in preterm neonates.¹⁴⁻¹⁷ How these therapies would interplay

with the influence of a synthetic surfactant versus animal-derived surfactants on reintubation rates is currently unknown.

Due to both pharmacoeconomic and pharmacodynamic considerations, an institution's formulary is typically limited to a single surfactant product. Most clinicians consider differences in safety and efficacy to be of primary importance in surfactant selection. Surfactants, probably the most widely studied pharmaceutical products in neonatal medicine, have shown multiple beneficial effects including decreased oxygen and ventilatory requirements, decreased pulmonary air leaks, and reductions in RDS and RDS-related deaths, yet one product does not consistently stand out as therapeutically superior based on available clinical data.² To date, poractant has demonstrated reduced mortality compared to beractant,¹⁸ and lucinactant has demonstrated reduced mortality compared to the combination of colfosceril and beractant.⁸ However, the conclusion that lucinactant reduces mortality compared to animal-derived surfactants has been criticized due to the relatively brief and subjective assessment in SELECT (i.e., RDS-related deaths at 14 days, whereas mortality at 36 weeks' post-menstrual age is generally considered to be the more clinically relevant outcome).¹⁹ In addition, the 1-year follow-up included the STAR trial, designed for noninferiority and underpowered due to early termination.¹¹ Likewise, reduced mortality with lucinactant was found only if infants with missing outcomes were treated as deaths. Due to conflicting mortality data, most clinicians would next consider differences in pulmonary morbidity to be of primary clinical significance. Unfortunately, the available surfactant products have not reduced rates of BPD in infants born at <30 weeks' gestation,² leaving reduction in total duration of mechanical ventilation as the primary outcome of interest. Although the initial extubation rates were similar in the SELECT and STAR trial, lucinactant was reported to have a significantly lower reintubation rate.¹³ However, the effect of any agent on the need for mechanical ventilation or reintubations must be considered in light of institutional ventilatory management practices. Large-scale research on the combined influence of surfactant agent and current ventilatory management is still needed.

Experts agree that when pulmonary surfactants are used by medical personnel with the necessary

expertise to administer and monitor therapy, they are safe and generally well-tolerated. The most common concerns related to tolerability are the transient events observed during drug administration, which are often related to dosing volume. Of the available surfactants, lucinactant has the largest dosing volume (5.8 mL/kg vs. 1.25-4 mL/kg for animal-derived surfactants). In SELECT, administration-related adverse events tended to be higher with lucinactant and beractant than with colfosceril and included transient pallor, dose interruption, and endotracheal obstruction.⁵ These events may potentially be minimized by giving the drug in four rather than two aliquots,⁵ but this practice will lengthen administration time. Questions have also been raised regarding exposure to microbial contamination or proinflammatory mediators associated with administration of animal-derived surfactants.² Although these issues are addressed by the use of a synthetic surfactant, there are also concerns with this type of product until its metabolic fate is better elucidated.²

Other considerations when selecting a surfactant product include dosing frequency and ease of administration. An ideal surfactant would be administered at extended intervals and have minimal storage and preparation requirements. Although all available surfactants require refrigeration, lucinactant must undergo a 15-minute warming procedure to 44°C in a dry block heater followed by cooling to body temperature,⁵ prolonging the time to administration of the first dose. Whereas surfactant prophylaxis is currently defined as administration within 10 to 30 minutes after birth, most centers strive for a window of <15 minutes. After cooling, lucinactant is only stable for 2 hours and cannot be returned to refrigeration.⁵ Other surfactants are typically warmed in the hand and can be returned to refrigeration within 24 hours. Dosing guidelines for lucinactant indicate that up to four doses may be given at intervals as frequent as every 6 hours within the first 48 hours of life,⁵ whereas poractant and calfactant are typically limited to three doses given every 12 hours. Studies have shown a reduction in redosing with poractant when used in preterm infants at recommended treatment doses.¹⁸ This has a potential for cost savings in terms of both product usage and manpower.

In this age of cost containment, no formulary

decision can be made without comparing the cost of competing drug products. Lucinactant therapy has been reported to be cost-effective compared with beractant and poractant.^{9,12} Ultimately, the cost of surfactant for a particular institution will be derived from a multitude of factors that are not generalizable from current clinical research, including cost variance between centers based on contract pricing and the use of surfactants for indications other than RDS, which may require larger doses for which vial sizes are not tailored. In addition, although not FDA-approved, some institutions dispense multiple doses from single-use vials. Lucinactant's shorter stability and inability to return to refrigeration may preclude this practice, thereby increasing its cost.

In summary, the available literature supports the fact that the newly approved second-generation synthetic surfactant lucinactant is equally effective as animal-derived surfactants. There are intriguing trends that allude to the possibility of advantages in duration of mechanical ventilation, reintubation rates, cost savings, and mortality. Future studies are needed that compare long-term morbidity and mortality rates in larger patient populations in order to validate these results. These trials would ideally incorporate more current ventilatory management practices including use of prophylactic caffeine and early NCPAP, as well as further defining the tolerability and metabolic fate of lucinactant.

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ABBREVIATIONS NCPAP, nasal continuous positive airway pressure; RDS, respiratory distress syndrome; SELECT, Safety and Effectiveness of Lucinactant versus Exosurf in a Clinical Trial; STAR, Surfaxin in Therapy Against RDS; VLBW, very low birth weight

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