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Review article

Lucinactant: A new solution in treating neonatal respiratory distress syndrome NRDS

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ABSTRACT

Lucinactant is a novel synthetic surfactant, approved by the FDA on March 6th 2012, for use in treatment of RDS. It's superiority as compared to the previously approved surfactants lie in containing sinapultide, a 21-amino acid peptide also known as KL_4 peptide, which has been designed to mimic the activity of human surfactant protein. Lucinactant is completely devoid of any animal derived components. It is the fifth drug approved by the FDA for the treatment of RDS. It has shown immense efficacy in phase two clinical trials and animal model studies and exhibited better efficiency when compared to other surfactants in both 24 hour and two week mortality rates of infants in RDS. Lucinactant tends reduce the surface tension at the air-liquid interface of alveolar surfaces and allows lungs to function normally. It was observed that the side effects were lesser with Lucinactant when compared with other naturally derived surfactants.

Keywords: Lucinactant, surfactant, RDS, Sinapultide.

INTRODUCTION

In preterm infants one of the major causes of morbidity and mortality is the respiratory failure secondary to the deficiency of surfactants. RDS was first characterized as surfactant deficiency disease of the newborn by Avery and Mead in 1959. [4] In neonates the Respiratory Distress Syndrome is caused by the incomplete development of lungs, observed in the birth of pre term infants sometimes it can also be genetic. Generally pre term infants are infants born prior to 37 weeks of gestation, but surfactant trials with preterm infants have included those between 23 and 34 weeks' gestation and/or with birth weights between 500 and 2000 grams since this deficiency is caused by the presence of immature type II pneumocytes which are only capable of producing surfactants after 20 weeks of gestation. Respiratory insufficiency in both term and preterm neonates leads to multi organ dysfunction; it was observed that the main cause of this was the deficiency or absence of surfactants which are a mixture of phospholipids, neutral lipids and protein and it reduces the surface tension in the alveolar spaces by acting at the air liquid interface. The administration of exogenous surfactants in such cases enabled the fetal lungs to not only recycle this surfactant but also enhanced the lung maturity and surfactant production, hence making the surfactant replacement therapy to be highly beneficial. Surfactant therapy substantially reduces mortality and respiratory morbidity for this population[1]. Surfactant replacement was established as an effective and safe therapy for immaturity-related surfactant deficiency by the early 1990s [2]. Study of various clinical trials has

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provided evidence that the use of surfactant therapy tends to increase the survival rate of these infants without any increment on the risk of occurrence of long term disabilities. Thus, surfactant replacement is associated with an absolute increase in the number of preterm infants who survive with and without disabilities. [3]

The first clinical use of exogenous surfactant to treat RDS was by Fujiwara and colleagues in 1980 [5] Since 1989, several animal derived surfactant preparations have been developed, each surfactant being more concentrated and tending to have a more rapid onset and longer duration of action. [6] But the mortality and morbidity due to RDS was still a leading cause of concern. The first synthetic containing peptide surfactant, Lucinactant was approved by FDA on March 6, 2012. Discovery labs evaluate about its commercial availability in 2012. [7] It is hoped that the development of protein-containing synthetic surfactant, such as lucinactant, will rival the efficacy of natural surfactants, but without the risks of their possible side effects. [8]

Lucinactant, is the novel synthetic surfactant containing sinapultide, which is an engineered peptide that imitates the action of human surfactant protein B. It tends to work by lowering the surface tension in the lungs and also by, enhancing the ability of the surfactant to spread better. Lucinactant is generally well tolerated. Adverse effects are transient and related to the administration procedure. [9] In addition; it may have an inherent and distinct ability to modulate lung inflammation. [10] Its superior activity as compared to the previously used animal derived natural surfactant is mainly attributed to the presence of sinapultide. Uniformity of surfactant distribution has been shown to improve as the volume of surfactant administered is increased. [11] The improvement in expansion pattern is suggestive of more uniform distribution of the surfactant that is likely reflective of the relatively higher dosing volume of lucinactant as compared with both animal derived surfactants. [12]

The incidence of RDS was compared and observed after 24 hours in preterm neonates receiving lucinactant and synthetic non-protein containing surfactants in a randomized, prophylaxis double blinded trial and it was observed that the rate was considerably lower in patients receiving lucinactant. In another similar trial the rate of survival of neonates with RDS without bronchopulmonary dysplasia was observed after 28 days, and lucinactant was not found to be inferior to the other synthetic surfactant used.

The pharmacological data on lucinactant was collected by performing in vitro studies or observing pulmonary function studies on animals, hence there is a lack of knowledge regarding the pharmacokinetic behavior of lucinactant. The distribution and absorption from the lungs into the systemic circulation as well as its clearance is still unknown. Similarly, the metabolic providence of sinapultide is still unclear.

DISCUSSION

Lucinanctant, previously known as KL_4 surfactant, is a novel drug used in the treatment of RDS in preterm neonates. Preceding the approval of lucinactant, the FDA had approved the use of three other surfactants; Colfosceril[13], was a synthetic non protein containing surfactant whereas Poractant α[14] and Beractant[15] were both animal derived surfactants. Although these animals' derived surfactants showed satisfactory results in the patients the predicament lied with the low level of proteins that they carried and the presence of risk of disease transmission whereas the synthetic surfactant contained only the phospholipids but lacked the surface proteins. Evidence suggested that synthetic surfactants consisting solely of phospholipids can be improved through the addition of peptides, such as sinapultide, that mimic the action of human surfactant protein-B (SP-B). SP-B is elaborately involved in supporting the ventilation in alveoli. Due to its slight hydrophobic property it helps in formation of a surface active film which tends to lower the surface tension. It also plays a fundamental role in maturation of surfactant. A synthetic surfactant containing a mimic of SP-B may also reduce the potential risks associated with the use of animal-derived products [16]. The exclusivity of lucinactant among other surfactants lies in the presence of sinapultide, which imitates the action and function of SP-B, and hence helps in avoiding the complications and mortality associated with its defficiency.

Three phase II studies have been conducted on infants at high risk of RDS [17] and another phase II study in infants with BPD, in order to compare and establish the efficacy of Lucinactant as compared to the previously used surfactants where it has shown greater or equivalent effectiveness. However the role of lucinactant in the study conducted on

adults with ARD's showed inconclusive or ineffective results.

In order to study the pharmacokinetics of the drug in vitro models were prepared due to the inherent intricacies of primary human lung cell cultures and whole animal studies. The Cultured Human Airway Epithelial Cells (Calu-3) model is an *in vitro* model developed to study the mechanism of hyperoxia or positive pressure induced lung injury [18] and to evaluate any new therapies which mimics the human respiratory function, structure and inflammatory responses. The studies conducted on this model showed lucinactant to be more protective than other animal derived surfactants. However the pharmacokinetic and pharmacodynamic understanding is still an ongoing process, owing to the obvious impediments involved in studying the distribution, metabolism and excretion pattern of the drug within the actual sample population of RDS. Though, the FDA recognizes that since the well-established preterm lamb model represents an acceptable animal model of RDS, this model could serve as an alternative to a clinical trial in human preterm infants[19]and the pre clinical carried on such models were considered to provide sufficient evidence for the approval of the use of lucinactant. The actual knowledge regarding the fate of the drug in the human body is still an area of interest and is being explored. Further studies and development of techniques to achieve a complete understanding is of high beneficence in order to ensure long term safety and complete evaluation of the lucinactant.

Specific surfactants are considered not only in term of the clinical but also in terms of the pharmacoeconomic outcomes, so as to assess the value of each product in the class since with the continous rise in the healthcare cost economic evaluation of therapies has become an integral part of the clinical decision process. The reintubations and consequent Mechanical ventilation (MV) are not only allied with increased mortality and morbidities but also an increase in hospital and individual expenditure. A recently published study showed that reintubation with MV was administered in 35% to 47% of preterm infants treated with exogenous surfactant and appears to be an independent risk factor predictive of major morbidity and mortality [20]. The morbidities due to MV include pneumonia, sepsis and BPD whereas extended placement of enotracheal tubes or repetitive intubations may lead to bradycardia, subglottic stenosis or tracheomalacia. Studies conducted by comparing the reintubation rates between infants receiving different surfactants showed a significant decrease with the use of lucinactant and a substantial cost saving. This decline in the reintubation rates with lucinactant was attributable to SP-B like activity of sinapultide. Lucinactant is not only more resistant to plasma proteins and oxidants but also modulates the inflammatory process in lungs [21].

The American Association for Respiratory Care (AARC) clinical practice guidelines 2013 for the use of surfactant therapy provide the administration, prophylaxis, administration, multiple dose strategy and preparations for all surfactants used in RDS. Prophylactic administration is for preterm infants who are believed to be at high risk for developing RDS while therapeutic administration for full term or pre term infants who are suspected to have a surfactant deficiency. However these guidelines contradict the use of surfactants in case of congenital anomalies incompatible with life beyond the neonatal period, respiratory distress in spite of mature lungs in infants and diagnosis of congenital diaphragmatic hernia. It is also essential to establish valid indications for administration. Natural surfactants are preferred over the synthetic ones as they shown better surface absorption and better lowering of surface tension, whereas the synthetic surfactant Lucinactant tend to show better batch control with lesser variation. These guidelines also accentuate the use of multi dose strategy rather than a single dose strategy.

Lucinatant is an equally potent therapeutic option as the animal derived surfactants although the lack of pharmacokinetic and pharmacodynamic data on lucinactant does not ascertain the efficacy of one class of surfactant over another at this point. Global research on the various aspects of administration, pharmacoeconomics and pharmacological facets should be supported in order to establish the most efficacious treatment plan to counter neonatal respiratory distress syndrome NRDS[23].

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