Drugs of the Future 2004, 29(6): 570-573

CCC: 0377-8282/2004

Lucinactant

USAN

Agent for Respiratory Distress Syndrome
Agent for Meconium Aspiration Syndrome
Lung Surfactant

ATI-02
KL4-surfactant
Surfaxin®

Humanized, engineered version of natural human lung surfactant based on the 21-amino-acid peptide KL4, palmitoyl-oleoylphosphatidylglycerol (POPG), palmitic acid and dipalmitoyl phosphatidylcholine (DPPC)

A surfactant formulation containing a mixture of synthetic phospholipids, fatty acid and synthetic peptide. Lucinactant is comprised of sinapultide, colfosceril palmitate (dipalmitoylphosphatidylcholine [DPPC]), palmitoyloleaylphosphatidyl glycerol sodium salt (POPG) and palmitic acid

EN: 257956

Abstract

The development of products for surfactant replacement therapy for the treatment of serious respiratory disorders such as acute respiratory distress syndrome (ARDS) and meconium aspiration syndrome (MAS) has been based on extracts from porcine or bovine lungs, but these products present a number of disadvantages. Thus, the search for safer surfactants which mimic natural human pulmonary surfactant continues. Lucinactant (KL4-surfactant, Surfaxin®) is a novel humanized, engineered version of natural human lung surfactant that is based on the 21-amino-acid peptide KL4 (sinapultide). It was designed to mimic the essential endogenous human surfactant protein B (SP-B). Lucinactant has been shown to have antiinflammatory properties, is resistant to proteolytic degradation and oxidation, and has no potential for transmitting animal-derived diseases. Lucinactant has proven safe and effective in the prevention of RDS in preterm infants and as a treatment for MAS in full-term infants and for adult ARDS. Lucinactant continues to undergo phase III development for the treatment of RDS in premature infants and MAS in full-term infants, as well as phase II development for the treatment of adult ARDS and the prophylaxis of MAS in full-term infants. An NDA has been filed for lucinactant for the prevention of RDS in premature infants.

Introduction

Pulmonary surfactant is a lipoprotein complex that is produced naturally in the lungs, where it lines the alveolar epithelium and serves to reduce surface tension, which facilitates alveoli expansion and allows gas exchange. Human surfactants contain phospholipids, predominantly dipalmitoylphosphatidylcholine (DPPC), in addition to surfactant proteins A, B, C and D. Surfactant is also a physical barrier to inhaled particle and noxious agents, enhances particle clearance, is involved in host defense against infection and possesses antiinflammatory properties.

Several serious respiratory disorders have been associated with a loss or lack of endogenous surfactant. Acute respiratory distress syndrome (ARDS) and meconium aspiration syndrome (MAS) are two such life-threatening disorders for which no specific therapy exists to reduce the associated morbidity and mortality, although numerous therapeutic strategies have been employed. Meconium aspiration syndrome is characterized by progressive respiratory distress, hypoxia, hypercapnia and acidosis, and its development can be due to mechanical airways obstruction, inflammatory cell infiltration, release of vasoconstrictive substances and inflammatory mediators, protein leakage into airways and meconium-induced inactivation of surfactant. It is estimated that about 25,000 newborn infants in the U.S. develop MAS each year and mortality rates for the disorder range from approximately 3% to 12%. Acute respiratory distress syndrome is characterized by noncardiogenic pulmonary edema and refractory hypoxemia, and involves injury to the alveolar-capillary barrier, lung inflammation, surfactant dysfunction and intrapulmonary shunting. It can be associated with systemic events such as sepsis, nonthoracic trauma, acute pancreatitis, major surgery, multiple blood transfusions, fat embolism or shock. The fatality rate for ARDS ranges from 40% to 60% (1-7).

Symptoms of ARDS and MAS include shortness of breath, chest tightening and loss of pulmonary function (*e.g.*, alterations in FEV_1, FVC, PO_2 and PCO_2).

L.A. Sorbera, P.A. Leeson. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-lysine

Fig. 1. Structure of sinapultide.

Research suggests that instillation of exogenous surfactant or surfactant replacement therapy would be an effective approach for the treatment of these respiratory disorders. To date, however, the development of products for surfactant replacement therapy has been based on extracts from porcine or bovine lungs and these products present a number of disadvantages, including limited supply, variation in content, problems in formulation, the risk of exposure to animal-derived diseases and the potential for immunogenicity of animal protein. Moreover, RDS is the only indication being treated today with approved surfactants (8, 9). Thus, the search for safer surfactants which mimic natural human pulmonary surfactant continues.

One product with particular promise is lucinactant (KL4-surfactant, Surfaxin®), a humanized, engineered version of natural human lung surfactant based on the 21-amino-acid peptide sinapultide (KL4, Fig. 1) and designed to mimic the endogenous human surfactant protein B (SP-B), which is essential for respiratory function through its ability to reduce surface tension and promote oxygen exchange. Lucinactant is an aqueous suspension that consists of KL4, dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoylphosphatidylglycerol (POPG) and palmitic acid. Lucinactant can be produced consistently in large quantities and can be formulated as an instillate, wet aerosol or dry powder aerosol. In addition, it has been shown to have antiinflammatory properties, is resistant to proteolytic degradation and oxidation, and has no potential for the transmission of animal-derived diseases. Lucinactant was therefore selected for further development for the prevention and treatment of MAS in full-term infants, RDS in premature infants and ARDS in adults (9).

Pharmacological Actions

The effects and uptake of lucinactant (0.01-1 mg/ml for up to 4 days) and its protein component KL4 (0.3-30 μg/ml for up to 4 days) were examined *in vitro* using primary cultures of human fetal pulmonary type II cells and human pulmonary adenocarcinoma cells (A549, NCI-H441). Results showed that lucinactant was taken up by all pulmonary cell types. Neither lucinactant nor KL4 alone significantly affected levels of surfactant protein SP-A, SP-B or SP-C mRNA in fetal human type II cells. Cells incubated in the presence of high concentrations of lucinactant had an increased number of lamellar bodies, an organelle involved in the storage and secretion of surfactant. However, the morphology of these lamellar bodies was not altered by treatment. Results suggest that lucinactant does not alter cell function (10-12).

The efficacy of lucinactant was demonstrated *in vivo* in several animals models of respiratory disorders.

Lucinactant significantly suppressed acute lipopolysaccharide (LPS)- and hyperoxia-induced lung injury in mouse models of RDS. When administered as a bolus (100 μl; 20 mg/ml 1, 3 and 19 h after LPS challenge) intranasally to mice with LPS-induced lung injury, lucinactant significantly reduced leukocyte influx into bronchoalveolar lavage (BAL) and total polymorphonuclear cell (PMN) counts at 24 h post-LPS. Treatment with lucinactant also tended to decrease the LPS-induced injurious response, as indicated by lower BAL protein levels. Thus, lucinactant significantly reduced neutrophil influx into alveoli and partially inhibited lung injury (13). Similarly, an intranasal bolus of lucinactant (100 μl; 20 mg/ml on days 3-6) given to mice subjected to hyperoxia-induced lung injury blocked neutrophil influx into alveoli and significantly inhibited acute lung injury according to acute lung injury scores, histopathology, leukocyte and PMN counts, and protein levels in BAL on day 7 (14).

The efficacy of lucinactant administered as a bolus (100 mg/kg divided between right and left sides) or as 2 bronchoalveolar lavages (2.5 and 10 mg/ml, 20 ml/kg divided between left and right sides, resulting in an average of 92 mg/kg in the lungs) at 3-5 h postinjury was compared in a rabbit model of ARDS (partial removal of intrinsic surfactant by 5 lavages and instillation of LPS). Bolus administration of the agent resulted in a rise in PaO_2 to > 300 mmHg over a 1-2-h period, with partial expansion of lungs; large areas of atelectasis were still evident with treatment. In contrast, administration of lucinactant by lavage resulted in a rapid and sustained increase in PaO_2 to > 300 mmHg and uniform expansion of the lungs. In addition, markedly reduced inflammatory exudate (*i.e.*, microscopic evaluation, protein levels, PMN counts) was detected in air-expanded alveoli and *post mortem* BAL fluid (15).

Lucinactant administered as a diluted lung lavage (16 ml/kg of 10 mg/ml) was also shown to be superior to bolus instillation (6 ml/kg of 30 mg/ml) in significantly improving gas exchange in an experimental model of MAS in newborn lambs. Administration of meconium resulted in severe hypoxia, hypercapnia and acidosis. However, treatment with lucinactant as a lavage resulted in significantly higher PaO_2 (163 mmHg *vs.* 78 mmHg) and pH, and lower $PaCO_2$ (30 mmHg *vs.* 50 mmHg) as compared to the group receiving lucinactant as a bolus (16).

A study conducted in preterm infant rhesus monkeys (127-131 days of gestation) which are deficient in pulmonary surfactant, resulting in severe RDS, demonstrated the efficacy of lucinactant (99, 133 or 200 mg/kg by instillation shortly after cesarean birth) in inducing alveolar expansion and normal function. Treatment with the agent induced a rise in the arterial to alveolar PaO_2 ratio (a/A) from 0.11 ± 0.01 before treatment to 0.40 ± 0.02 at 12-13 h posttreatment. This increase was sustained

throughout the study period, so that the mean a/A at 22-23 h was 0.45 ± 0.07. Moreover, the atelectasis observed prior to treatment was reversed. Animals treated with the highest dose of lucinactant displayed a faster, more consistent and better response. Control animals treated with surfactant lacking the KL4 peptide had a mean a/A of 0.15 ± 0.03 at 9 h of age as compared to 0.38 ± 0.02 in animals treated with lucinactant. No alterations in physiological, hematological or biochemical parameters were observed with treatment (17). In another study also using a preterm (127-130 days) infant rhesus monkey model of RDS, intrapulmonary distribution of lucinactant was shown to be more homogeneous when the agent was administered using an adapter permitting maintenance of positive end-expiratory pressure as compared to administration by instillation with disconnection from mechanical ventilation (18).

A study examining the influence of lucinactant formulation on the output rate from several nebulizers showed that the formulation can be optimized for the nebulizer being used. In this study, novel formulations of lucinactant were prepared (*e.g.*, low ionic strength, reduced viscosity), nebulized using the Aeroneb® professional nebulizer, an air-jet nebulizer and ultrasonic nebulizers, and the output rates were compared. The standard formulation of lucinactant was best aerosolized using Aeroneb® (19).

Clinical Studies

An open-label, uncontrolled phase Ib trial in 12 adults with ARDS examined the safety and tolerability of sequential bronchopulmonary segmental lavage with lucinactant (group 1: 30-ml aliquot of 2.5 mg/kg/segment followed by 2 x 30-ml aliquots of 10 mg/ml; group 2: 2 x 30-ml aliquots of 2.5 mg/ml followed by lavage with 10 mg/ml; group 3: same as group 2 with possible repeated dosing 6-24 h later). All dosing regimens were well tolerated, with no serious adverse events reported. At 96 h after treatment, decreases in the fraction of inspired oxygen (FiO_2) (from 0.80 to 0.52 for all patients) and positive end-expiratory pressure (from 10.3 cm H_2O to 7.6 cm H_2O for all patients) were observed. Protein analysis of BAL samples from 4 patients in group 3 who received a second course of lucinactant showed a reduction in protein concentration at the time of retreatment in 18 of 22 fluid samples (20).

The safety and efficacy of lucinactant (2 instillations of 8 ml/kg of 2.5 mg/ml into each lung over about 20 s followed by suctioning after 5 ventilator breaths and a third lavage with 10 mg/ml) were compared with standard therapy (*e.g.*, oxygen and conventional positive-pressure ventilation and use of alkalosis, paralysis, vasopressors or sedation) in a multicenter, randomized, open-label, controlled phase I/II trial in 22 newborn infants (gestational age of at least 35 weeks) with MAS. Lucinactant was concluded to be safe and generally well tolerated. Trends were observed for lucinactant-treated infants to be weaned from mechanical ventilation sooner (6.3 days *vs.* 9.9 days) and to have a more rapid decrease in oxygenation (persisting for 96 h) as compared to infants treated with standard therapy, although statistical significance was not reached. No significant differences in the number of hospitalizations or the number or type of intercurrent illnesses, including respiratory illnesses, were observed in patients at follow-up through 1 year of age (21).

A multicenter, randomized phase III trial in 1,294 premature infants examined the safety and efficacy of lucinactant prophylaxis as compared to the non-protein-containing synthetic surfactant Exosurf® as a treatment for RDS; the cow-derived surfactant Survanta® was used as a reference arm in the trial. An independent safety monitoring board reported that statistical significance was achieved in favor of lucinactant for the coprimary endpoints of RDS-related mortality through 14 days of life and the incidence of RDS at 24 h of life (22, 23).

Another multicenter, randomized phase III trial conducted in 243 infants compared the safety and efficacy of lucinactant with the animal-derived surfactant portactant alfa (Curosurf®) in preventing RDS in very preterm infants (gestational age = 24- < 29 weeks). At the end of the trial, 37.8% of the lucinactant-treated infants were alive with no signs of bronchopulmonary dysplasia as compared to 33.1% of those administered portactant alfa. No significant differences were observed between groups at 28 days in frequency of oxygen desaturation, bradycardia, apnea, bronchopulmonary dysplasia, mortality, air leaks, pulmonary hemorrhage or sepsis. In addition, no differences were noted between treatment groups in neurodevelopmental or respiratory outcomes at 6 and 12 months. It was concluded that both agents were safe and comparably effective (24).

Lucinactant continues to undergo phase III development for the treatment of RDS in premature infants and MAS in full-term infants, and phase II development for the treatment of ARDS in adults and for the prevention of MAS in full-term infants. An NDA has been filed in the U.S. seeking approval for lucinactant in the prevention of RDS in premature infants and an MAA for this same indication is being prepared in Europe (22).

Sources

Originated at the Scripps Research Institute, La Jolla, CA (US); licensed to Discovery Laboratories, Inc. (US) and sublicensed to Laboratorios del Dr. Esteve, SA (ES) for Southern Europe and Latin America.

References

1. Wiswell, T.E., Bent, R.C. *Meconium staining and the meconium aspiration syndrome. Unresolved issues.* Pediatr Clin North Am 1993, 40: 955-81.

2. Cleary, G.M., Wiswell, T.E. *Meconium-stained amniotic fluid and the meconium aspiration syndrome. An update.* Pediatr Clin North Am 1998, 45: 511-29.

3. Moses, D., Holm, B.A., Spitale, P., Liu, M.Y., Enhorning, G. *Inhibition of pulmonary surfactant function by meconium.* Am J Obstet Gynecol 1991, 164: 477-81.

4. Brandstetter, R.D., Sharma, K.C., DellaBadia, M., Cabreros, L.J., Kabinoff, G.S. *Adult respiratory distress syndrome: A disorder in need of improved outcome.* Heart Lung 1997, 26: 3-14.

5. Fulkerson, W.J., MacIntyre, N., Stamler, J., Crapo, J.D. *Pathogenesis and treatment of the adult respiratory distress syndrome.* Arch Intern Med 1996, 156: 29-38.

6. Kollef, M.H., Schuster, D.P. *The acute respiratory distress syndrome.* New Engl J Med 1995, 332: 27-37.

7. Sachdeva, R.C., Guntupalli, K.K. *Acute respiratory distress syndrome.* Crit Care Clin 1997, 13: 503-21.

8. Merritt, T.A., Soll, R., Hallman, M. *Overview of exogenous surfactant replacement therapy.* J Intesive Care Med 1993, 8: 205-28.

9. *Product development.* Discovery Laboratories Web Site April 20, 2004.

10. Alcorn, J.L., Moya, F.R. *The effect of Surfaxin® and KL-4 peptide on surfactant protein gene expression cell physiology of human type II cells.* Pediatr Res 2000, 47(4, Part 2): 350A.

11. Romero, E.J., Alcorn, J.L., Moya, F.R. *The interaction and physiological effects of Surfaxin® on fetal human pulmonary type II cells in primary culture.* J Perinat Med 2001, 29(Suppl. I): 90.

12. Romero, E.J., Alcorn, J.L., Moya, F.R. *The interaction and physiological effects of Surfaxin® (lucinactant) on fetal human pulmonary type II cells.* Pediatr Res 2002, 51(4, Part 2): 345A.

13. Christofidou-Solomidou, M., Stephens, S., Lau, K., Arguiri, E., Bohen, A., Christie, J., Niven, R., Segal, R. *Humanized lung surfactant (KL4-surfactant) mitigates LPS-induced lung injury in mice.* FASEB J 2003, 17(5, Part 2): Abst 556.4.

14. Christofidou-Solomidou, M., Argyris, E., Bohen, A., Stephens, S., Niven, R., Segal, R. *Humanized lung surfactant (KL4-surfactant) prevents hyperoxic acute lung injury in mice.* 99th Int Conf Am Thorac Soc (May 16-21, Seattle) 2003, A179.

15. Cochrane, C.G., Revak, S.D. *Surfactant lavage treatment in a model of respiratory distress syndrome.* Chest 1999, 116(1, Suppl.): 85S-6S.

16. Valls-i-Soler, A., Gastiasoro, E., Rey, C., Arnaiz, A., Roman, L., Alfonso, L.F., Gastiasoro, L., Loreiro, B.,Perez, J., Alvarez, F.J. *Experimental meconium aspiration in newborn lambs. Comparative effects of bolus and bronchoalveolar lavage with Surfaxin®.* Pediatr Res 2003, 53(4, Part 2): 435A.

17. Revak, S.D., Merritt, T.A., Cochrane, C.G., Heldt, G.P., Alberts, M.S., Anderson, D.W., Kheiter, A. *Efficacy of synthetic peptide containing surfactant in the treatment of respiratory distress syndrome in preterm infant rhesus monkeys.* Pediatr Res 1996, 39: 715-2.

18. Merritt, T.A., Kheiter, A., Cochrane, C.G. *Positive end-expiratory pressure during KL4 surfactant instillation enhances intrapulmonary distribution in a simian model of respiratory distress syndrome.* Pediatr Res 1995, 38: 211-7.

19. Watanabe, W., Bhargava, Y., Patel, N., Rairkar, M., Nivel, R.W. *The effect of lung surfactant formulation on the output rate from several nebulizers.* J Aerosol Med 2003, 16(2): Abst 36.

20. Wiswell, T.E. Smith, R.M., Katz, L.B. et al. *Bronchopulmonary segmental lavage with Surfaxin (KL4-surfactant) for acute respiratory distress syndrome.* Am J Respir Crit Care Med 1999, 160: 1188-95.

21. Wiswell, T.E., Knight, G.R., Finer, N.N. et al. *A multicenter, randomized, controlled trial comparing Surfaxin (lucinactant) lavage with standard care for treatment of meconium aspiration syndrome.* Pediatrics 2002, 109: 1081-7.

22. *NDA filing for Surfaxin for RDS in premature infants.* DailyDrugNews.com (Daily Essentials) April 19, 2004

23. *Positive phase III topline results for Surfaxin in RDS.* DailyDrugNews.com (Daily Essentials) December 1, 2003.

24. Sinha, S., Soler, A.V.I., Lacaze-Masmonteil, T., Gadzinowski, J., Segal, R., D'Agostino, R., Wiswell, T., Massaro, J. *Randomised controlled trial of a new surfactant, Surfaxin® (lucinactant) v Curosurf® (poractant alfa) for the prevention of RDS in very preterm babies.* Arch Dis Child 2004, 89(Suppl. 1): Abst G5.

Additional References

Manalo, E., Merritt, T.A., Kheiter, A., Amirkhanian, J., Cochrane, C. *Comparative effects of some serum components and proteolytic products of fibrinogen on surface tension-lowering abilities of beractant and a synthetic peptide containing surfactant KL4.* Pediatr Res 1996, 39: 947-52.

Manalo, E., Merritt, T.A., Amirkhanian, J.D., Kheiter, A. *Characterization of surfactant subtypes of beractant and a synthetic peptide containing surfactant KL4 following surface area cycling and addition of fibrinogen.* Lung 1997, 175: 225-33.

Wiswell, T.E., the Surfaxin-Lavage for MAS Trial Group. *Bronchoalveolar lavage with dilute Surfaxin™ (KL4-surfactant) for the management of the meconium aspiration syndrome (MAS).* Pediatr Res 1999, 45(4, Part 2): 326A.

Wiswell, T.E., the Surfaxin™ for ARDS Trial Group. *Bronchopulmonary segmental lavage with Surfaxin™ (KL4-surfactant) for acute respiratory distress syndrome (ARDS).* Am J Respir Crit Care Med 1999, 159(3, Part 2): A378.

Discovery commences pivotal phase III trial of Surfaxin in infants with MAS. DailyDrugNews.com (Daily Essentials) February 1, 2000.

FDA okays Discovery's phase II trial with Surfaxin. DailyDrugNews.com (Daily Essentials) November 21, 2000.

Discovery Laboratories begins phase III IRDS trial for Surfaxin. DailyDrugNews.com (Daily Essentials) April 6, 2001.

EMEA awards orphan product status to Surfaxin for MAS. DailyDrugNews.com (Daily Essentials) August 13, 2001.

Results from phase III Surfaxin trial will be delayed several months. DailyDrugNews.com (Daily Essentials) February 25, 2003.

Enrollment concluded in supportive phase III trial of Surfaxin for RDS. DailyDrugNews.com (Daily Essentials) June 10, 2003.

Surfaxin selected for CMA Pilot 2 Program. DailyDrugNews.com (Daily Essentials) February 24, 2004.

Sinapultide equivalent to poractant alfa in the prevention of RDS. DailyDrugNews.com (Daily Essentials) April 28, 2004.

Valls-i-Soler, A., Gastiasoro, E., Rey, C., Arnaiz, A., Alvarez, F.J. *Comparative effects of lucinactant (Surfaxin(R) vs. a porcine surfactant on pulmonary gas exchange and mechanics in premature lambs.* Pediatr Res 2003, 53(4, Part 2): 511A.