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New Synthetic Surfactant – How and When?

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Abstract

Animal-derived surfactant preparations are very effective in the treatment of premature infants with respiratory distress syndrome but they are expensive to produce and supplies are limited. In order to widen the indications for surfactant treatment there is a need for synthetic preparations, which can be produced in large quantities and at a reasonable cost. However, development of clinically active synthetic surfactants has turned out to be more complicated than initially anticipated. The hydrophobic surfactant proteins, SP-B and SP-C, which are involved in the adsorption of surface-active lipids to the air-liquid interface of the alveoli and increase alveolar stability, are either too big to synthesize, structurally complex or unstable in pure form. A new generation of synthetic surfactants containing simplified phospholipid mixtures and small amounts of peptides replacing the hydrophobic proteins is currently under development and will in the near future be introduced into the market. However, more trials need to be performed before any conclusions can be drawn about the effectiveness of these synthetic surfactants in relation to natural animal-derived preparations.

Introduction

Surfactant deficiency in preterm babies causes respiratory distress syndrome (RDS). This disease can now be successfully treated by airway instillation of exogenous surfactants and the best results have been obtained with preparations purified from animal lungs, in some cases modified by addition of specific lipids. There has always been a concern about the potential risk of immunogenic and infectious complications using animal-derived surfactant preparations but after treatment of millions of infants no adverse effects of this nature have been described [1]. However, these surfactant preparations are expensive to produce and supplies are limited so there is a need to develop synthetic surfactants, which can be produced in large quantities at a reasonable cost.

The composition of pulmonary surfactant is very complex containing at least 50 different lipids [2] and four specific proteins – SP-A, SP-B, SP-C and SP-D [3]. The predominant surfactant component is the surface-active dipalmitoylphosphatidylcholine which is responsible for surface tension reduction to low values during expiration. Surfactant preparations purified from animal lungs by extraction with organic solvents contain this great variety of phospholipids and the two hydrophobic proteins SP-B and SP-C which are critical for the adsorption and spreading of the surfactant film at the air-liquid interface [3].

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Synthesis of Surfactant Components

Development of clinically active synthetic surfactants has turned out to be more complicated than initially anticipated [4]. First, the complexity of the composition of phospholipids makes it difficult if not impossible to synthesize them all at a reasonable cost. Second, SP-B is too big and structurally complex to be synthesized by organic chemical methods and the expression of functionally active recombinant SP-B has not been reported. Third, SP-C is extremely hydrophobic and especially in pure form structurally unstable.

Incomplete knowledge of the function of some phospholipids in surfactant, in combination with limited commercial availability of many synthetic phospholipids, has resulted in the use of very simple phospholipid mixtures in synthetic surfactant preparations. Increased understanding of the molecular mechanism involved in formation and preservation of the surfactant film at the alveolar surface has led to the development of stable and rather simple peptides to replace native SP-B and SP-C.

Peptides in Surfactants

Various molecules have been designed to substitute for the hydrophobic surfactant proteins SP-B and SP-C [5–20]. Recently, non-natural bioinspired structures based on poly-*N*-substituted glycines (peptoids) with α-chiral side chains have been created to mimic both the SP-B fragment SP-B_{1-25} [6] and the SP-C analogue SP-C(Leu) [7]. These non-natural molecules in a lipid mixture improve surface pressure-area isotherms, surfactant film morphology and dynamic adsorption, and decrease minimum and maximum surface tension during cycling in the pulsating bubble surfactometer. However, no data from in vivo studies with these synthetic surfactants have been published.

KL_4 is a 21-residue peptide which was designed to mimic the structure of SP-B [8] in particular SP-B(64–79) with the intermittent basic residues and the multiplicity of leucines in the hydrophobic stretches being near duplicates of the C-terminus of SP-B [9]. In contrast to the helix of SP-B(64–79) with its amphipathic surface, the KL_4 peptide presents its positive charges distributed over the entire helical circumference [10]. The surface structure of KL_4 thus differs from that of SP-B and segments thereof and also from SP-C with an α-helix with exclusively unpolar residues [10].

Several peptides covering different parts of SP-B have been synthesized and their biophysical and physiological activities in different lipid mixtures have been evaluated in vitro and in vivo. N-terminal fragments of SP-B, especially residues 1–25, seem to mimic many of the in vitro activities of native SP-B [11] and a dimeric counterpart, dSP-B_{1-25}, enhances surface properties compared to monomeric SP-B_{1-25} [12]. A disulfide-linked construct based on the primary structures of the N- and C-terminal domains of SP-B (Mini-B) forms charged amphipathic helices and reproduces key in vitro and in vivo functions of full-length SP-B [13].

Synthetic surfactant based on recombinant SP-C but lacking the palmitoyl chains is highly effective at restoring lung function in surfactant-deficient animals [14]. Modification of the structure by replacing Cys4 and Cys5 with Phe, and Met32 with Ile gives a synthetic surfactant that improves lung function in premature newborn rabbits and lambs [15] as well as in animal models of acute lung injury [16]. Since the poly-valyl sequence in SP-C does not favor helix conformation, analogues with substitutions in this region have been designed. Replacement of the poly-valyl part of SP-C with a poly-leucyl stretch produces an analogue which forms an α-helix [17–19]. However, this analogue has a strong tendency for peptide oligomerization. The problem was circumvented by synthesizing an SP-C analogue (SP-C33) with one positive charge in the N-terminal part of the α-helical chain. SP-C33 in phospholipid mixtures can be suspended and administered at a concentration of 80 mg/ml. In preterm rabbit fetuses it increases lung compliance to levels similar to those obtained with commercially available modified natural surfactant preparations currently used for treatment of clinical RDS [20].

Physiological Effects

The physiological effects of synthetic surfactant preparations have been assessed in both premature animals with surfactant deficiency [14, 15, 19–24] and in animals with acute respiratory distress syndrome (ARDS) [11, 13, 25–27]. Various animal models have been used but in contrast to natural surfactant preparations, synthetic surfactants seem to need positive end-expiratory pressure (PEEP) for surfactant response [15]. This indicates that natural surfactant preparations are more effective in stabilizing the airways. However, ventilation with PEEP is part of the routine management of patients with severe respiratory failure.

The efficacy of different surfactant preparations is difficult to compare in many studies using small groups of animals with large individual responses. In a recent study using 6 premature lambs with a gestational age of 135 days (term 145 days) in each treatment group, the conclusion was stated that lucinactant (Surfaxin) and poractant-alfa (Curosurf) produced similar improvements in gas exchange and lung mechanics even though 2 of the 6 animals did not respond to Surfaxin and the mean value of PaO_2 in this group was about 35% lower and the mean airway pressures higher than those for the Curosurf-treated lambs [23]. With small studies such as this, statistically significant differences in treatment efficacy will be virtually impossible to demonstrate. Thus, adequate sample sizes are needed to discover if different surfactant preparations have similar effects or they differ.

Two synthetic preparations have been used in clinical trials, recombinant SP-C (rSP-C) surfactant (Venticute) [28, 29] and Surfaxin [30–33]. Surfactant based on rSP-C improves lung function in different animal models [14–16, 27]. However, no results from clinical trials in preterm babies with RDS have been published and treatment with Venticute in patients with ARDS did not improve survival but had a positive effect on gas exchange [27, 28]. The other peptide-containing synthetic surfactant, Surfaxin, was given as prophylactic treatment to premature infants in two randomized clinical trials [30, 31]. In the study comparing Surfaxin and beractant (Survanta) the Surfaxin group was twice as large as the Survanta group [30]. The other study comparing Surfaxin and Curosurf was stopped when half the sample size had been recruited [31]. Larger studies are needed to conclude if Surfaxin is as effective as the natural surfactant preparations to prevent RDS in preterm babies. Surfaxin forms a gel that requires heating at 44°C for 15 min and subsequent shaking before tracheal administration [23, 30, 31]. This may make it difficult to use Surfaxin as an emergency therapy. Furthermore, cooling of Surfaxin after the heating procedure to body or room temperature may increase the risk of gel formation which may result in plugging of the tracheal tube or the airways. Thus, the physical properties of surfactant preparations are important to avoid negative effects during treatment of patients.

Concluding Remarks

Intensive research has provided increased understanding of molecular mechanisms of various surfactant components. These efforts have led to the development of peptides which may mimic the functions of the hydrophobic proteins SP-B and SP-C. New synthetic surfactant preparations based on these peptides and synthetic lipids will probably reach the market in the near future and may eventually replace natural surfactant preparations. In contrast to natural surfactant preparations, these synthetic surfactants seem to be physiologically active only during ventilation with PEEP but in patients with severe respiratory failure this type of ventilation is part of routine management. Thus, well-defined synthetic surfactants with good physiological activity and allowing production in large amounts at a reasonable cost are a prerequisite to use surfactant treatment for various lung diseases with inadequate surfactant function or as carrier for different drugs.

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References

1 Kattwinkel J: Synthetic surfactants: the search goes on. Pediatrics 2005;115:1075–1076.

2 Berggren P, Curstedt T, Grossmann G, Nilsson R, Robertson B: Physiological activity of pulmonary surfactant with low protein content: effect of enrichment with synthetic phospholipids. Exp Lung Res 1985;8:29–51.

3 Johansson J, Curstedt T: Molecular structures and interactions of pulmonary surfactant components. Eur J Biochem 1997;244:675–693.

4 Curstedt T, Johansson J: New synthetic surfactants – basic science. Biol Neonate 2005;87: 332–337.

5 McLean LR, Lewis JE, Krstenansky JL, Hagaman KA, Cope AS, Olsen KF, Matthews ER, Uhrhammer DC: An amphipathic α-helical decapeptide in phosphatidylcholine is an effective synthetic lung surfactant. Am Rev Respir Dis 1993;147:462–465.

6 Seurynck SL, Patch JA, Barron AE: Simple, helical peptoid analogues of lung surfactant protein B. Chem Biol 2005;12:77–88.

7 Wu CW, Seurynck SL, Lee, KYC, Barron AE: Helical peptoid mimics of lung surfactant protein C. Chem Biol 2003;10:1057–1063.

8 Cochrane CG, Revak SD: Pulmonary surfactant protein B (SP-B): structure-function relationships. Science 1991;254:566–568.

9 Merritt TA: Concerning the article by T. Curstedt and J. Johansson: New synthetic surfactants – basic science. Biol Neonate 2006;89: 257–258.

10 Curstedt T, Johansson J: Letter to the editor – reply. Biol Neonate 2006;89:258–259.

11 Gupta M, Hernández-Juviel JM, Waring AJ, Bruni R, Walther FJ: Comparison of functional efficacy of surfactant protein B analogues in lavaged rats. Eur Respir J 2000;16:1129–1133.

12 Veldhuizen EJA, Waring AJ, Walther FJ, Batenburg JJ, van Golde LMG, Haagsman HP: Dimeric N-terminal segment of human surfactant protein B (dSP-B_{1-25}) has enhanced surface properties compared to monomeric SP-B_{1-25}. Biophys J 2000;79:377–384.

13 Waring AJ, Walther FJ, Gordon LM, Hernandez-Juviel JM, Hong T, Sherman MA, Alonso C, Alig T, Braun A, Bacon D, Zasadzinski JA: The role of charged amphipathic helices in the structure and function of surfactant protein B. J Peptide Res 2005;66:364–374.

14 Hawgood S, Ogawa A, Yukitake K, Schlueter M, Brown C, White T, Buckley D, Lesikar D, Benson B: Lung function in premature rabbits treated with recombinant human surfactant protein-C. Am J Respir Crit Care Med 1996; 154:484–490.

15 Davis AJ, Jobe AH, Hafner D, Ikegami M: Lung function in premature lambs and rabbits treated with a recombinant SP-C surfactant. Am J Respir Crit Care Med 1998;157:553–559.

16 Häfner D, Germann PG, Hauschke D: Comparison of rSP-C surfactant with natural and synthetic surfactants after late treatment in a rat model of the acute respiratory distress syndrome. Br J Pharmacol 1998;124:1083–1090.

17 Takei T, Hashimoto Y, Aiba T, Sakai K, Fujiwara T: The surface properties of chemically synthesized peptides analogous to human pulmonary surfactant protein SP-C. Biol Pharm Bull 1996;19:1247–1253.

18 Takei T, Hashimoto Y, Otsubo E, Sakai K, Ohkawa H: Characterization of poly-leucine substituted analogues of the human surfactant protein SP-C. Biol Pharm Bull 1996;19:1550–1555.

19 Nilsson G, Gustafsson M, Vandenbussche G, Veldhuizen E, Griffiths WJ, Sjövall J, Haagsman HP, Ruysschaert JM, Robertson B, Curstedt T, Johansson J: Synthetic peptide-containing surfactants. Evaluation of transmembrane versus amphipathic helices and SP-C poly-valyl to poly-leucyl substitution. Eur J Biochem 1998;255:116–124.

20 Johansson J, Some M, Linderholm BM, Almlén A, Curstedt T, Robertson B: A synthetic surfactant based on a poly-Leu SP-C analog and phospholipids: effects on tidal volumes and lung gas volumes in ventilated immature newborn rabbits. J Appl Physiol 2003;95: 2055–2063.

21 Merritt TA, Kheiter A, Cochrane CG. Positive end-expiratory pressure during KL$_4$ surfactant instillation enhances intrapulmonary distribution in a simian model of respiratory distress syndrome. Pediatr Res 1995;38:211–217.

22 Revak SD, Merritt TA, Cochrane CG, Heldt GP, Alberts MS, Anderson DW, Kheiter A: Efficacy of synthetic peptide-containing surfactant in the treatment of respiratory distress syndrome in preterm infant rhesus monkeys. Pediatr Res 1996;39:715–724.

23 Gastiasoro-Cuesta E, Alvarez-Diaz FJ, Rey-Santano C, Arnaiz-Renedo A, Loureiro-Gonzalez B, Valls-i-Soler A: Acute and sustained effects of lucinactant versus poractant-α on pulmonary gas exchange and mechanics in premature lambs with respiratory distress syndrome. Pediatrics 2006;117:295–303.

24 Michna J, Jobe AH, Ikegami M: Positive end-expiratory pressure preserves surfactant function in preterm lambs. Am J Respir Crit Care Med 1999;160:634–639.

25 Balaraman V, Meister J, Ku TL, Sood SL, Tam E, Killeen J, Uyehara CFT, Egan E, Easa D: Lavage administration of dilute surfactants after acute lung injury in neonatal piglets. Am J Respir Crit Care Med 1998;158:12–17.

26 Walther FJ, Hernández-Juviel JM, Gordon LM, Waring AJ, Stenger P, Zasadzinski JA: Comparison of three lipid formulations for synthetic surfactant with a surfactant protein B analog. Exp Lung Res 2005;31:563–579.

27 Spragg RG, Smith RM, Harris K, Lewis J, Häfner D, Germann P: Effect of recombinant SP-C surfactant in a porcine lavage model of acute lung injury. J Appl Physiol 2000;88:674–681.

28 Spragg RG, Lewis JF, Wurst W, Häfner D, Baughman RP, Wewers, MD, Marsh JJ: Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. Am J Respir Crit Care Med 2003;167: 1562–1566.

29 Spragg RG, Lewis JF, Walmrath HD, Johannigman J, Bellingan G, Laterre PF, Witte MC, Richards GA, Rippin G, Rathgeb F, Häfner D, Taut FJH, Seeger W: Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. N Engl J Med 2004;351:884–892.

30 Moya FR, Gadzinowski J, Bancalari E, Salinas V, Kopelman B, Bancalari A, Kornacka MK, Merritt TA, Segal R, Schaber CJ, Tsai H, Massaro J, d'Agostino R for the International Surfaxin Collaborative Study Group: A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. Pediatrics 2005;115:1018–1029.

31 Sinha SK, Lacaze-Masmonteil T, Valls-i-Soler A, Wiswell TE, Gadzinowski J, Hajdu J, Bernstein G, Sanchez-Luna M, Segal R, Schaber CJ, Massaro J, d'Agostino R for the Surfaxin Therapy Against Respiratory Distress Syndrome Collaborative Group: A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics 2005;115:1030–1038.

32 Wiswell TE, Smith RM, Katz LB, Mastroianni L, Wong DY, Willms D, Heard S, Wilson M, Hite RD, Anzueto A, Revak SD, Cochrane CG: Bronchopulmonary segmental lavage with surfaxin (KL$_4$ surfactant) for acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160:1188–1195.

33 Wiswell TE, Knight GR, Finer NN, Donn SM, Desai H, Walsh WF, Sekar KC, Bernstein G, Keszler M, Visser VE, Merritt TA, Mannino FL, Mastrioianni L, Marcy B, Revak SD, Tsai H, Cochrane CG: A multicenter, randomized, controlled trial comparing surfaxin (lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. Pediatrics 2002;109:1081–1087.