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(72) Feltaláló(k): HERTING, Egbert, I-43100 Parma (IT) GOPEL, Wolfgang, I-43100 Parma (IT) CHIESI, Paolo, I-43100 Parma (IT)	(74) Képviselő: dr. Török Ferenc, DANUBIA Szabadalmi és Jogi Iroda Kft., Budapest

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(54) **A METHOD OF ADMINISTRATION OF A PULMONARY SURFACTANT**

VERFAHREN ZUR VERABREICHUNG EINES LUNGENSURFACTANTS

PROCÉDÉ D'ADMINISTRATION D'UN SURFACTANT PULMONAIRE

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(73) Proprietor: **CHIESI FARMACEUTICI S.p.A.**
43100 Parma (IT)

(72) Inventors:
• **HERTING, Egbert**
I-43100 Parma (IT)
• **GOPEL, Wolfgang**
I-43100 Parma (IT)
• **CHIESI, Paolo**
I-43100 Parma (IT)

(74) Representative: **Minoja, Fabrizio**
Bianchetti Bracco Minoja S.r.l.
Via Plinio, 63
20129 Milano (IT)

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Description

FIELD OF INVENTION

[0001] The present invention concerns a method for preventing and/or treating respiratory distress syndrome in infants in need of such treatment, the method comprising intratracheal administration of a pulmonary surfactant by a thin tub as well as a kit comprising said pulmonary surfactant and tube.

BACKGROUND OF THE INVENTION

[0002] The human lung is composed of a large number of small air sacs, called alveoli, in which gases are exchanged between the blood and the air spaces of the lungs. In healthy individuals, this exchange is mediated by the presence of a protein-containing surfactant complex that prevents the lungs from collapsing at the end of expiration.

[0003] Lung surfactant complex is composed primarily of lipids and contains minor amounts of various proteins. An absence of adequate levels of this complex results in malfunction of the lung. This syndrome is called Respiratory Distress Syndrome (RDS) and is the single most important cause of morbidity and mortality in pre-term infants.

[0004] RDS is mainly treated with replacement therapy whereby exogenous pulmonary surfactant preparations extracted from animal lungs, known as modified natural surfactants are administered to the human in need. For instance, modified natural surfactants used in the clinical practice are poractant alfa derived from porcine lung, and sold under the trademark of Curosurf®, beractant (Surfacten® or Survanta®), bovactant (Alveofact®), both derived from bovine lung, and calfactant derived from calf lung (Infasurf®).

[0005] Synthetic surfactants mimicking the composition of the modified natural surfactants, and known as reconstituted surfactants, have also been developed.

[0006] Exogenous pulmonary surfactants are currently administered by endotracheal instillation as suspension in a saline aqueous solution to intubated pre-term infants kept under intermittent positive pressure ventilation (IPPV).

[0007] However, IPPV is in itself an invasive procedure which frequently requires supplemental medication like treatment with sedatives, analgesic agents and catecholamines.

[0008] Furthermore IPPV in pre-term infants with RDS has long been recognized to contribute to lung injury which may lead to the development of pneumothorax and/or bronchopulmonary dysplasia (BDP); and may cause reduction of mucociliary clearance, mucosal injury, and secondary infections as well as blockage of the endotracheal.

[0009] In view of the potential complications associated with intubation and mechanical ventilation, attention

has been focused on different approaches of administration of exogenous surfactant.

[0010] Since long time, as a possible initial respiratory support for very low birth weight (VLBW) infants, use of early nasal Continuous Positive Airway Pressure (nCPAP), that delivers air into the lungs through specially designed nasal devices such as masks, prongs or tubes, has been introduced in neonatal intensive care.

[0011] Recently, to give exogenous surfactant without mechanical ventilation, the use of a thin gastric tube placed in the trachea supported with nCPAP has been proposed (Göpel W et al, Abstract presented at the 20th International Workshop on Surfactant Replacement, Belfast, June 2-5, 2005, page 12: Kribs, A et al. Paediatr Anaesth. 2007 Apr;17(4):364-9).

[0012] In particular, Göpel W and colleagues reported the administration of 60 mg bovine surfactant, diluted to 30 mg/ml, by a 5 Fr gastric tube in spontaneously breathing infants with a mean weight of about 1 kg.

[0013] However, to improve the clinical outcome, an initial dose higher than 60 mg/kg body weight is currently recommended. A dose higher than 60 mg/kg requires the use of a higher concentration of the surfactant preparation, in particular of at least 40 mg/ml.

[0014] Since viscosity increases with surfactant concentration, the administration of a concentration of at least 40 mg/ml by means of a gastric tube having a very small diameter (5 Fr. corresponds to about 1.7 mm) would only be possible with a surfactant having low viscosity. In fact high viscosities would make the passage of the surfactant through the gastric tube and the small airways more difficult and may therefore result in uneven distribution in the lungs of the pre-term infants. Theoretically, surfactants having high viscosities involve the risk of blockage of the gastric tube and of acute airway obstruction.

[0015] In view of the drawbacks of the known methods for delivery of exogenous surfactant, alternative therapeutic methods for surfactant administration are needed. Such methods should provide at least identical or, preferably improved clinical outcome, without the potential complications associated with endotracheal intubation and mechanical ventilation.

[0016] The therapeutic methods and kits disclosed herein provide a remarkable improvement over known therapies.

SUMMARY OF THE INVENTION

[0017] The present invention concerns a pharmaceutical composition comprising at least 40 mg/ml of a pulmonary surfactant suspended in not more than 3.0 ml of a pharmaceutically acceptable aqueous medium, having a viscosity lower than 20 mPas for use for the prevention and/or treatment of a patient suffering of a respiratory distress syndrome to which nasal Continuous Positive Airway pressure with a nasal device is applied at a pressure from 1 to 12 cm water, wherein said composition is

administered into the trachea of said patient by a tube having a diameter of 5 Fr that is removed at the end of administration.

DEFINITION

[0018] As used herein, the term "modified natural pulmonary surfactant" means a lipid extract of minced mammalian lung which, due to the lipid extraction step used in the manufacture process, is deprived of the hydrophilic proteins SP-A and SP-D and contains variable amounts of the hydrophobic proteins SP-B and SP-C. Depending on the method of extraction, the preparation may contain non-surfactant lipids and other components.

[0019] As used herein, the term "reconstituted pulmonary surfactant" means a synthetic surfactant made of a mixture of polar lipids, primarily phospholipids and optionally other components such as neutral lipids to which have been added surfactant proteins/peptides isolated from animals or proteins/peptides manufactured through recombinant technology such as those described in WO 95/32992, or synthetic surfactant protein analogues such as those described in WO 89/06657, WO 92/22315 and WO 00/47623.

[0020] "Pharmaceutical acceptable" is a term used herein that refers to a medium that does not produce an allergic or similar untoward reaction when administered to an infant.

[0021] As used herein, the expression "improving the clinical outcome" means a surfactant with an improved efficacy in terms of indices of activity, i.e. lung compliance, lung gas volume, blood gases and ventilator settings.

DETAILED DISCLOSURE OF THE INVENTION

[0022] The present invention discloses a composition for use in a method of preventing and/or treating a respiratory distress syndrome in a patient in need of such treatment, said method comprises the steps of:

- a) applying nasal Continuous Positive Airway Pressure (nCPAP) with a nasal device to said patient at a pressure of about 1 to 12 cm water;
- b) administering a pulmonary surfactant suspended in a pharmaceutically acceptable aqueous medium via a tube having a diameter of 5 Fr into the trachea of said patient; and
- c) removing said tube at the end of the administration;

wherein the pulmonary surfactant suspension is applied at a concentration of at least 40 mg/ml and has a viscosity lower than 20 mPas.

[0023] Advantageously, the composition of the invention is applied to pre-term infants, and preferably pre-term very-low-birth-weight-infants of 24-35 weeks gestational age that are spontaneously breathing, and dem-

onstrate early signs of respiratory distress syndrome as indicated either by clinical signs and/or supplemental oxygen demand (fraction of inspired oxygen (FiO_2) > 30%). The treatment shall start preferably in the first 24h of life.

[0024] The composition of the invention is directed to the prevention and/or treatment of the respiratory distress syndrome on the infant related to a surfactant-deficiency or dysfunction (RDS) as well as of conditions in which respiratory distress may be present that include, but are not limited to, meconium aspiration and pulmonary infection.

[0025] The composition of the invention may also be useful for preventing and/or treating acute respiratory distress syndrome in children or adults.

[0026] The composition of the invention is applied nasally by Continuous Positive Airway Pressure (nCPAP) with a nasal device such as a mask, prongs, or a pharyngeal tube according to known procedures.

[0027] Preferably, a nasal mask is utilised. Any nasal mask commercially available may be used, for example those provided by The CPAP Store LLC and the CPAP Company.

[0028] Nasal CPAP is typically applied at a pressure comprised between 1 and 12 cm water, preferably 2 and 8 cm water, although the pressure can vary depending on the infant and the pulmonary condition.

[0029] The application of nCPAP is advantageously carried out to the infant prior to administering the pulmonary surfactant and continuously throughout the procedure during both the administering and the removing steps.

[0030] Optionally, prior to the procedure, atropine is administered i.v. at 5 $\mu\text{g/kg}$ body weight. Sedative and/or analgesic drugs can also optionally be administered.

[0031] Before administering the pulmonary surfactant, the gastric tube is placed with a Magill-forceps under direct visualization of the vocal cords of the infants by means of a laryngoscope.

[0032] After placement of the gastric tube, the laryngoscope is removed and the pulmonary surfactant is administered by instillation in the trachea at controlled rate with a suitable device.

[0033] The pulmonary surfactant in the form of suspension is administered by means of a tube having a diameter of 5 Fr.

[0034] Any gastric or nasogastric tube, arterial or suction catheter of common use in hospitals can be utilised for the purpose of the invention.

[0035] The tube may be made of any material, preferably of polyurethane or silicone.

[0036] A 5 Fr tube is used because it has a small diameter, but at the same time it is stiff enough to allow easy introduction with the Magill forceps. Preferably, a cm-scale is marked on the tube to allow the correct length of introduction.

[0037] If the tube has side holes, such holes should not be too far away from the catheter tip. The connector to the syringe should be small too avoid unnecessary

dead space.

[0038] Preferably, the tube has a total length of about 30 cm to allow a length of about 10 cm in the oral cavity/nasopharynx and a length of about 20 cm outside for easy handling.

[0039] Suitable devices include syringes having a small dead volume, preferably of less than 0.5 ml, more preferably of less than 0.3 ml or infusion pumps.

[0040] Depending on the volume to be administered, the skilled person shall control the rate of delivering of the device in such a way as to instil the surfactant in a time comprised between 1 and 5 minutes, preferably between 1 and 3 minutes.

[0041] The pulmonary surfactant is administered as a suspension in a sterile pharmaceutically acceptable aqueous medium, preferably in a buffered physiological saline (0.9% w/v sodium chloride) aqueous solution, more preferably buffered at a pH comprised between 5.5 and 6.5.

[0042] The concentration of the surfactant is of at least 40 mg/ml, preferably comprised between 40 and 80 mg/ml.

[0043] The applied volume should be not more than 3.0 ml, preferably not more than 2 ml and, depending on the concentration of the pulmonary surfactant and dead volume the syringe.

[0044] Any modified natural or reconstituted pulmonary surfactant can be used provided that the relevant suspension in an aqueous medium has a viscosity lower than 20 mPas (1 mPas corresponds to 1 centipoise), preferably comprised between 5 and 15 mPas, more preferably between 6 and 10 mPas.

[0045] The viscosity may be determined by any known method. Preferably, the viscosity is determined according to the method reported in Example 1.

[0046] In particular, it has been found that, due to its low viscosity, the modified natural pulmonary surfactant known as poractant alfa is particularly suitable for administration by a gastric tube.

[0047] In particular its low viscosity allows administering the surfactant at a concentration of at least 40 mg/ml.

[0048] Poractant alfa formulated as a sterile suspension in a saline (0.9% w/v sodium chloride) aqueous solution at a concentration of 80 mg/ml is commercially available under the trademark of Curosurf®.

[0049] To achieve a concentration of 40 mg/ml or others comprised in the range of 40 to 80 mg/ml, Curosurf® can be diluted with a suitable volume of saline aqueous solution.

[0050] Advantageously, the dose of the pulmonary surfactant to be administered is equal to or higher than 80 mg *per* kg body weight, preferably comprised between 100 and 200 mg *per* kg body weight. The preferred dose is 100 mg *per* kg body weight.

[0051] The dose of the pulmonary surfactant to be administered varies with the size and maturity of the patient, as well as with the severity of the patient's condition. The skilled persons will be readily able to determine these

factors and to adjust the dosage administered via the thin tube.

[0052] After administration of pulmonary the surfactant, the thin tube is removed.

[0053] However, the patient may receive a second dose of pulmonary surfactant, depending on the severity of the individual condition and on the response to the first surfactant treatment. In particular, if the needed FiO_2 is higher than 40%, the surfactant can be instilled by the thin tube, otherwise if the needed FiO_2 exceeds 60%, the surfactant can be instilled by endotracheal intubation under mechanical ventilation.

[0054] Said second dose may be equal to, higher or lesser than the first dose, depending on the needs and response of the patient.

[0055] The present invention is also directed to a kit comprising: a) a pharmaceutical composition comprising a pulmonary surfactant suspended in a pharmaceutically acceptable aqueous medium at a concentration of at least 40 mg/ml, said composition having a viscosity lower than 20 centipoise; b) a thin tube having a diameter comprised between 5 and 12 Fr; c) a device for administering the surfactant at a controlled rate; and d) container means for the dosage form, the thin tube and the device.

[0056] The pulmonary surfactant is preferably poractant alfa.

[0057] The composition described herein is typically prepared by combining the pulmonary surfactant with a suitable volume of a pharmaceutically acceptable aqueous medium, preferably a saline aqueous solution, to form a substantially homogeneous aqueous suspension at the desired concentration.

[0058] Advantageously, the pharmaceutical composition is sterile and is supplied as a single-use glass vial.

[0059] Otherwise, in a particular embodiment, the sterile pharmaceutical composition may be supplied directly in the device used for administering the surfactant at a controlled rate.

[0060] The composition can be sterilized according to known methods.

[0061] The following examples illustrate the invention in more detail.

EXAMPLES

Example 1 - Viscosity measurement of a suspension of poractant alfa in a physiological saline aqueous solution

[0062] Rheological measurements are carried out at 25°C with a rheometer SR 200 (Rheometric Scientific) and 40 parallel plate geometry using different batches of Curosurf®, i.e. of poractant alfa suspended in physiological saline aqueous solution at a concentration of 80 mg/ml.

[0063] The instrument is calibrated to a gap of 0.7 mm.

[0064] The shear rate is varied between 0 and 500 s^{-1} .

[0065] For all batches Curosurf®, the viscosity (η) ap-

proaches a well-reproducible asymptotic value (max Shear Rate 500 s⁻¹) comprised between 6 and 10 mPas (1 mPas = 1 centipoise).

Example 2 - Administration of 100 mg/kg dose po-ractant alfa by gastric tube in very-low-birth-weight infants

Protocol of the study

[0066] In a preliminary observational study no differences between infants after surfactant application without intubation and infants with standard treatment are observed, despite the fact that infants treated with surfactant application without intubation are significantly smaller.

[0067] The primary objective of the following study is to demonstrate that the treatment of very-low-birth-weight (VLBW) infants with intratracheal instillation of a pulmonary surfactant is able to reduce the frequency of mechanical ventilation.

[0068] Secondary objectives of the study are to demonstrate that the proposed method:

- is associated with a reduced duration and intensity of mechanical ventilation; and
- is associated with a reduced incidence of bronchopulmonary dysplasia (BDP),

while being at least equivalent to standard treatment with regard to the secondary outcome measures death, intraventricular hemorrhage grade III and IV (IVH), and periventricular leukomalacia (PVL).

Design:

[0069] Prospective, randomized multi-center trial.

Study population:

[0070]

Inclusion criteria:

- gestational age 26+0 - 28+6 weeks,
- birth weight below 1500 gram
- Age 0-12 hours
- Informed consent

Exclusion criteria:

- Mechanical ventilation
- Participation in other studies

Intervention:

[0071]

Control-group:

- CPAP if FiO₂ exceeds 0.25
- all other therapies according to local standards.

Intervention group:

- CPAP if FiO₂ exceeds 0.25
- intratracheal surfactant via a gastric feeding tube if FiO₂ exceeds 0.3 (to keep oxygen saturation above 85%) and Silverman-score >4
- all other therapies according to local standards.

Intervention:

- Surfactant is given at a dose of 100 mg surfactant per kg body weight via a thin (gastric) tube into the trachea of the spontaneously breathing infant.
- CPAP is applied continuously during the procedure (nasal IPPV may be applied).
- Optional use of atropin (5 µg/kg body weight i.v.) prior to the procedure.
- As many doctors will not use sedation for intubation in the delivery suite or in the first hours/minutes of life, sedation/analgesia is not mandatory and at the discretion of the individual neonatologist.
- The gastric tube is placed with a Magill-forceps under direct visualization of the vocal cords by means of a laryngoscope.
- After placement of the gastric tube, the laryngoscope is removed and surfactant (100 mg/kg body weight) is instilled into the trachea during 1-5 minutes.
- Thereafter, the gastric tube is removed.
- Close observation of the child during the procedure is mandatory.
- Surfactant administration can be repeated if FiO₂ exceeds 0.4.
- Intubation and intratracheal surfactant administration should be considered if FiO₂ exceeds 0.6 or the child suffers from severe respiratory distress.
- All other treatments according to local standards.

Primary Outcome Measure:

- Intubation and mechanical ventilation between the 25. and 72. hour of life
- or
- FiO₂ >0.6 (to keep oxygen saturation above 85%) between the 25. and 72. hour of life
- or
- pCO₂ > 65 mm Hg for more than two hours between the 25. and 72. hour of life.

Sample size:

[0072] Based on current multi-center study data, we expect a frequency of the primary outcome measure in the control group of 60% vs. 40% in the intervention group. Since 50% of the infants are randomized to the control group, a total of 210 infants (105 in each group) will be necessary to test the primary hypothesis ($p=0,05$; beta-error 0,2; 2-sided). Since the participating centers are treating 250 patients/year who are eligible for the study and we calculated a 60% inclusion rate, a period of 30 months would be sufficient to test the primary hypothesis.

Secondary outcomes:

[0073] Ventilation rate, IVH, PVL, BPD, death, operation due to retinopathy (ROP), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intestinal perforation, hydrocephalus and ventricular-peritoneal-shunt, number of surfactant doses, total surfactant (mg/kg bodyweight), days on assisted ventilation, days on supplemental oxygen, duration of hospitalization, weight gain per day, pneumothorax, other complications of prematurity (same definitions as for the genetic study).

Methods against bias:

[0074] Infants are randomized prior to intubation. To avoid the possible bias that infants in the intervention group are not intubated although they meet local intubation criteria, we defined a combined primary endpoint using a $FiO_2 > 0.6$ to gain a saturation $> 85\%$ and/or $pCO_2 > 65$ mm Hg for more than two hours during the 25-72 hour of life as an indicator for treatment failure. FiO_2 -levels and pCO_2 levels are observed and documented by nurses. Blinding and a sham procedure in the control group are not possible.

Claims

1. A pharmaceutical composition comprising at least 40 mg/ml of a pulmonary surfactant suspended in not more than 3.0 ml of a pharmaceutically acceptable aqueous medium, having a viscosity lower than 20 mPas for use for the prevention and/or treatment of a patient suffering of a respiratory distress syndrome to which nasal Continuous Positive Airway pressure with a nasal device is applied at a pressure from 1 to 12 cm water, wherein said composition is administered into the trachea of said patient by a tube having a diameter of 5 Fr that is removed at the end of administration.
2. The pharmaceutical composition for use according to claim 1, wherein the concentration of the pulmonary surfactant is comprised between 40 and 80

mg/ml.

3. The pharmaceutical composition for use according to claim 1 or 2, wherein the pulmonary surfactant is administered at a dose equal to or higher than 80 mg per kg body weight.
4. The pharmaceutical composition for use according to claim 3, wherein the dose is comprised between 100 and 200 mg per kg body weight.
5. The pharmaceutical composition for use according to any preceding claim, wherein the volume of the pharmaceutically acceptable aqueous medium is not more than 2 ml.
6. The pharmaceutical composition for use according to any preceding claim, wherein the viscosity comprised between 5 and 15 mPas.
7. The pharmaceutical composition for use according to claim 6, wherein the viscosity is comprised between 6 and 10 mPas.
8. The pharmaceutical composition for use according to any preceding claim, wherein the pulmonary surfactant is a modified natural pulmonary surfactant or a reconstituted pulmonary surfactant.
9. The pharmaceutical composition for use according to claim 8, wherein the pulmonary surfactant is a lipid extract of minced mammalian lung deprived of the hydrophilic proteins SPA-A and SP-D and containing variable amounts of the hydrophobic proteins SP-B and SP-C.
10. The pharmaceutical composition for use according to claim 8, wherein the surfactant is poractant alfa.
11. The pharmaceutical composition for use according to any preceding claim, wherein the tube is selected from the group consisting of gastric tube, nasogastric tube, arterial catheter and suction catheter.
12. The pharmaceutical composition for use according to any one of the claims 1 to 11, wherein the respiratory distress syndrome is the infant respiratory distress syndrome.
13. The pharmaceutical composition for use according to any one of the claims 1 to 11, wherein the respiratory distress syndrome is due to meconium aspiration or pulmonary infection.

Patentansprüche

1. Pharmazeutische Zusammensetzung, die wenigstens

- tens 40 mg/ml eines pulmonalen Surfactant suspendiert in nicht mehr als 3,0 ml eines pharmazeutisch annehmbaren wässrigen Mediums umfasst, die eine Viskosität von niedriger als 20 mPas hat, zur Verwendung für die Prävention und/oder Behandlung eines Patienten, der an einem Atemnotsyndrom leidet, bei dem ein nasaler kontinuierlicher positiver Atemwegsdruck mit einer nasalen Vorrichtung mit einem Druck von 1 bis 12 cm Wasser angewandt wird, wobei die Zusammensetzung durch einen Schlauch mit einem Durchmesser von 5 Fr, der am Ende der Verabreichung entfernt wird, in die Trachea des Patienten verabreicht wird.
2. Pharmazeutische Zusammensetzung zur Verwendung gemäß Anspruch 1, wobei die Konzentration des pulmonalen Surfactant zwischen 40 und 80 mg/ml liegt.
 3. Pharmazeutische Zusammensetzung zur Verwendung gemäß Anspruch 1 oder 2, wobei das pulmonale Surfactant mit einer Dosis verabreicht wird, die gleich oder höher als 80 mg pro kg Körpergewicht ist.
 4. Pharmazeutische Zusammensetzung zur Verwendung gemäß Anspruch 3, wobei die Dosis zwischen 100 und 200 mg pro kg Körpergewicht liegt.
 5. Pharmazeutische Zusammensetzung zur Verwendung gemäß einem vorangehenden Anspruch, wobei das Volumen des pharmazeutisch annehmbaren wässrigen Mediums nicht mehr als 2 ml ist.
 6. Pharmazeutische Zusammensetzung zur Verwendung gemäß einem vorangehenden Anspruch, wobei die Viskosität zwischen 5 und 15 mPas liegt.
 7. Pharmazeutische Zusammensetzung zur Verwendung gemäß Anspruch 6, wobei die Viskosität zwischen 6 und 10 mPas liegt.
 8. Pharmazeutische Zusammensetzung zur Verwendung gemäß einem vorangehenden Anspruch, wobei das pulmonale Surfactant ein modifiziertes natürliches pulmonales Surfactant oder ein rekonstituiertes pulmonales Surfactant ist.
 9. Pharmazeutische Zusammensetzung zur Verwendung gemäß Anspruch 8, wobei das pulmonale Surfactant ein Lipidextrakt von zerkleinerter Säugetierlunge ist, dem die hydrophilen Proteine SPA-A und SP-D entzogen wurden und der variable Mengen der hydrophoben Proteine SP-B und SP-C enthält.
 10. Pharmazeutische Zusammensetzung zur Verwendung gemäß Anspruch 8, wobei das Surfactant Po-ractant alfa ist.
 11. Pharmazeutische Zusammensetzung zur Verwendung gemäß einem vorangehenden Anspruch, wobei der Schlauch aus der Gruppe, bestehend aus Magenschlauch, transnasaler Magensonde, arteriellem Katheter und Saugkatheter, ausgewählt ist.
 12. Pharmazeutische Zusammensetzung zur Verwendung gemäß einem der Ansprüche 1 bis 11, wobei das Atemnotsyndrom das Säuglingsatemnotsyndrom ist.
 13. Pharmazeutische Zusammensetzung zur Verwendung gemäß einem der Ansprüche 1 bis 11, wobei das Atemnotsyndrom durch Mekoniumaspiration oder pulmonale Infektion bedingt ist.

Revendications

1. Composition pharmaceutique comprenant au moins 40 mg/ml d'un surfactant pulmonaire en suspension dans pas plus de 3,0 ml d'un milieu aqueux pharmaceutiquement acceptable, ayant une viscosité inférieure à 20 mPas pour une utilisation prévue pour la prévention et/ou le traitement d'un patient souffrant d'un syndrome de détresse respiratoire, patient auquel est appliquée, avec un dispositif nasal, une pression positive continue dans les voies respiratoires nasales, à une pression de 1 à 12 cm d'eau, où ladite composition est administrée dans la trachée dudit patient, par une sonde ayant un diamètre de 5 Fr, sonde qui est retirée à la fin de l'administration.
2. Composition pharmaceutique pour une utilisation selon la revendication 1, dans laquelle la concentration du surfactant pulmonaire est comprise entre 40 et 80 mg/ml.
3. Composition pharmaceutique pour une utilisation selon la revendication 1 ou 2, dans laquelle le surfactant pulmonaire est administré à une dose égale ou supérieure à 80 mg par kg du poids du corps.
4. Composition pharmaceutique pour une utilisation selon la revendication 3, dans laquelle la dose est comprise entre 100 et 200 mg par kg du poids du corps.
5. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications précédentes, dans laquelle le volume du milieu aqueux pharmaceutiquement acceptable n'est pas de plus de 2 ml.
6. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications précédentes, dans laquelle la viscosité est comprise entre 5 et 15 mPas.

7. Composition pharmaceutique pour une utilisation selon la revendication 6, dans laquelle la viscosité est comprise entre 6 et 10 mPas.
8. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications précédentes, dans laquelle le surfactant pulmonaire est un surfactant pulmonaire naturel modifié ou un surfactant pulmonaire reconstitué. 5
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9. Composition pharmaceutique pour une utilisation selon la revendication 8, dans laquelle le surfactant pulmonaire est un extrait lipidique de poumon de mammifère émincé sans les protéines hydrophiles SPA-A et SP-D et contenant les protéines hydrophobes SP-B et SP-C en quantités variables. 15
10. Composition pharmaceutique pour une utilisation selon la revendication 8, dans laquelle le surfactant est du poractant alfa. 20
11. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications précédentes, dans laquelle la sonde est sélectionnée dans le groupe constitué d'une sonde gastrique, d'une sonde naso-gastrique, d'un cathéter artériel et d'un cathéter d'aspiration. 25
12. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications 1 à 11, où le syndrome de détresse respiratoire est le syndrome de détresse respiratoire du nouveau-né. 30
13. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications 1 à 11, où le syndrome de détresse respiratoire est dû à une inhalation méconiale ou à une infection pulmonaire. 35

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REFERENCES CITED IN THE DESCRIPTION

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Szabadalmi igénypontok

1. Gyógyszerészeti készítmény, amely tartalmaz pulmonális felületaktív anyagból legalább 40 mg/ml-t 3,0 ml-nél nem több gyógyszerészetileg elfogadható vizes közegben szuszpendálva, amelynek a viszkozitása 20 mPas-nál kisebb, légzőszervi distressz szindrómában szenvedő beteg esetében megelőzésben és/vagy kezelésben történő alkalmazásra, aki számára nazális folyamatos pozitív légúti nyomást alkalmazunk egy nazális eszközzel 1-12 cm víz nyomással, ahol a készítményt a beteg légcsővébe adjuk egy 5 Fr átmérővel rendelkező csővel, amit eltávolítottunk a beadás végén.
2. Gyógyszerészeti készítmény alkalmazásra az 1. igénypont szerint, ahol a pulmonális felületaktív anyag koncentrációja 40 mg/ml és 80 mg/ml közötti.
3. Gyógyszerészeti készítmény alkalmazásra az 1. vagy 2. igénypont szerint, ahol a pulmonális felületaktív anyagot 80 mg/testtömeg kg-mal egyenlő vagy ennél nagyobb dózisban adagoljuk.
4. Gyógyszerészeti készítmény alkalmazásra a 3. igénypont szerint, ahol a dózis 100 mg/testtömeg kg és 200 mg/testtömeg kg közötti.
5. Gyógyszerészeti készítmény alkalmazásra az előző igénypontok bármelyike szerint, ahol a gyógyszerészetileg elfogadható vizes közeg térfogata 2 ml-nél nem több.
6. Gyógyszerészeti készítmény alkalmazásra az előző igénypontok bármelyike szerint, ahol a viszkozitás 5 mPas és 15 mPas közötti.
7. Gyógyszerészeti készítmény alkalmazásra a 6. igénypont szerint, ahol a viszkozitás 6 mPas és 10 mPas közötti.
8. Gyógyszerészeti készítmény alkalmazásra az előző igénypontok bármelyike szerint, ahol a pulmonális felületaktív anyag módosított természetes pulmonális felületaktív anyag vagy rekonstitúált pulmonális felületaktív anyag.
9. Gyógyszerészeti készítmény alkalmazásra a 8. igénypont szerint, ahol a pulmonális felületaktív anyag SPA-A és SP-D hidrofíl proteinektől megfosztott és SP-B és SP-C hidrofób proteinekkel tartalmazó darált emlős tüdő lipid extraktuma.
10. Gyógyszerészeti készítmény alkalmazásra a 8. igénypont szerint, ahol a felületaktív anyag proaktáns alfa.
11. Gyógyszerészeti készítmény alkalmazásra az előző igénypontok bármelyike szerint, ahol a cső a következők alkotta csoportból választott: gyomorszonda, orrilegí cső, artériás katéter és szívó katéter.
12. Gyógyszerészeti készítmény alkalmazásra az 1-11. igénypontok bármelyike szerint, ahol a légzőszervi distressz szindróma újszülött légzőszervi distressz szindróma.
13. Gyógyszerészeti készítmény alkalmazásra az 1-11. igénypontok bármelyike szerint, ahol a légzőszervi distressz szindróma meconium aspiráció vagy pulmonális fertőzés következménye.