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All about ALVEOFACT

ALVEOFACT DESCRIPTION

1. What Alveofact is and what it is used for

Alveofact is a natural surfactant from bovine lung. Preventive use in premature neonates with a high risk of respiratory distress syndrome (RDS).

2. Before you use Alveofact

Do not use Alveofact

- If you are allergic (hypersensitive) to phospholipid fraction from bovine lung.

No substance-related contraindications are known so far.

Caution:

The benefits and risks of Alveofact therapy for congenital infections in premature neonates have not yet been adequately elucidated. The acute effect may be reduced if connatal pneumonia is suspected. Pulmonary function may also deteriorate in the event of concomitant un derdevelopment of the lung (prolonged deficiency of amniotic fluid due to ruptured membranes or congenital renal function impairment).

Take special care with Alveofact

Preclinical studies demonstrate that the body's own defence cells (scavenger cells, white blood cells) decompose lipid emulsions. This process may be impaired by Alveofact in the presence of lung infection and/or blood poisoning.

Alveofact may only be used if adequate facilities for ventilation and monitoring of premature neonates with respiratory distress syndromes are available. There have been singular case reports of obstruction of the tracheal tube by viscous material. The origin and composition of this material is unknown. Although a certain causal connection between the use of Alveofact and such a life threatening event has not been proven, it is important to heed the given instructions for use and storage. If obstruction of the tracheal tube is suspected, it is advised to aspirate the ventilation tubing and change the ventilation tube, respectively.

Using other medicines

No substance-related interactions are known so far.

No negative effects have been seen from Alveofact therapy following administration of ambroxol infusion concentrate or glucocorticoids to the mother prevent respiratory distress syndrome.

Important information about some of the ingredients of Alveofact

The pre-filled syringe with 1.2 ml solvent contains 0.078mmol (=1.8mg) sodium, thus less than 1 mmol (23 mg) sodium per pre-filled syringe(= single dose), i.e. almost free from sodium.

3. How to use Alveofact?

Always use Alveofact exactly as your doctor has told you. Use this medicine according to the following dosage recommendations.

A single dose of 1.2 ml Alveofact per kg body weight (equivalent to 50 mg total phospholipids per kg body weight), and application within the first hour after birth, are recommended.

Method and route of administration

Treatment with Alveofact is given only by endotracheopulmonary instillation.

The initial dose of Alveofact should be given as a bolus within the first hour after birth. A ready prepared catheter (e.g. umbilical catheter or gastric tube) is inserted through the positioned tracheal tube and the catheter opening positioned at the level of the tip of the tube. Using a syringe, the single dose of 1.2 ml Alveofact per kg body weight (corresponding to 50 mg total phospholipids per kg body weight) is administered as an intratracheal bolus via this catheter.

Additional injections of air are used to help ensure that instillation is complete. Upon removal of the catheter the patient is reconnected to the respirator. To promote the equal distribution of Alveofact, the patient may be gently turned from side to side every few seconds.

Duration of treatment

Depending on the need for ventilation, up to three subsequent applications of the same dose may be given following the initial dose. The total dose should not exceed 4 doses of 1.2 ml Alveofact per kg body weight (corresponding to 200 mg total phospholipids per kg body weight) within the first 5 days of life.

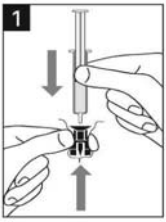
How should Alveofact be prepared for use?

There are two options:

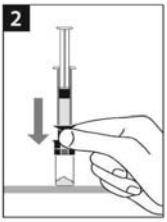
Option 1 - with vial adapter
Option 2 - with cannula

Option 1 - with vial adapter

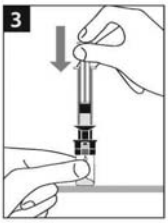
Caution. The syringe and vial adapter remain connected to the vial during the entire reconstitution procedure and are also used for removal of the reconstituted suspension.



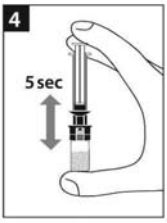
Open the top of the vial adapter pack. Position the cone of the syringe on the vial adapter.



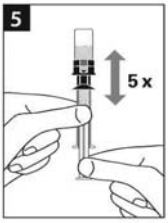
Push the tip of the vial adapter firmly into the rubber stopper until it is in place.



Add the solvent to the vial.

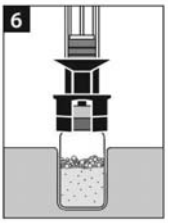


Then shake immediately for 5 seconds.



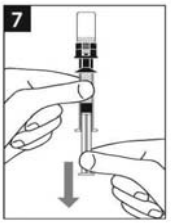
With the suspension inverted, withdraw it into the syringe and then inject it back into the vial.

Repeat 5 times!



Wait about one minute until the foam and suspension have separated.

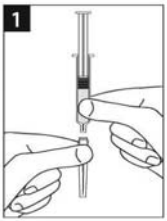
Recommendation: Use the holder enclosed in the pack!



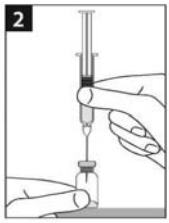
With the suspension inverted, withdraw it into the syringe and remove the syringe ready for administration. Residual foam will be left in the vial.

Option 2 - with cannula

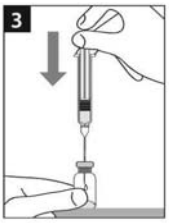
Caution. The syringe with cannula remains connected to the vial during the entire reconstitution process and is also used for removal of the reconstituted suspension.



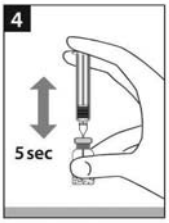
Open the top of the cannula pack. Place the cone of the syringe on the cannula.



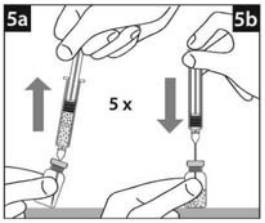
Insert the cannula into the vial through the rubber stopper.



Inject the solvent into the vial.

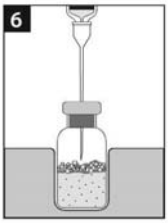


Then shake immediately for 5 seconds.



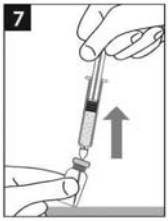
Holding the suspension at an angle, withdraw it into the syringe and then inject it back into the vial.

Thereafter remove the cannula from the suspension (but not from the vial) in order to prevent the suspension from rising into the syringe. Repeat this procedure a total of 5 times.



Wait about one minute until the foam and suspension have separated

Recommendation: Use the holder enclosed in the pack.



The suspension can be removed by slow withdrawal.

Residual foam will remain in the vial.

What must be remembered when using Alveofact Powder?

- Check that the application catheter is positioned correctly in the tracheal tube prior to administration of Alveofact.
- The partial pressure levels of carbon dioxide can change rapidly within the first hour of administration of Alveofact. It is therefore advantageous to ensure, by continual measurement of the partial pressure levels of carbon dioxide and oxygen through the skin or by repeat capillary blood gas analysis, that pronounced changes in carbon dioxide partial pressure are prevented by adjusting the respiratory parameters (peak inspiratory pressure, respiratory frequency).
- It must likewise be ensured, by adjusting the oxygen concentration in the inhaled air, that the partial pressure of arterial oxygen does not exceed the desired limits in order to prevent an increase in the risk of retinal injury in premature neonates.
- When using high-frequency mechanical ventilation (respiratory frequency above 60 per minute, exhalation time less than 0.6 seconds) it is essential to ensure that the exhalation period following Alveofact administration is sufficiently long. If the ventilation is not adapted in such way following of Alveofact, there is a risk of slowly increasing hyperdistension of the lung from "inadvertent or auto-PEEP": If passive exhalation is incomplete, the pressure in the lungs after exhalation will be higher than the setting on the respirator. The volume of gas which is found in the lung after normal exhalation may thereby rise pathologically. The inhalation pressures required for ventilation must then be inappropriately increased, thereby increasing the risk of pressure injury in the lungs.

- Until Alveofact has been fully distributed in the lungs, coarse inhalatory rhonchi can be auscultated from the rib cage in the first few minutes after administration. They are not an indication for tracheal aspiration, which otherwise may be done at any time.
- If the need for oxygen with normoventilation exceeds a level of 40%, up to three follow-up applications of 1.2 ml Alveofact per kg body weight (corresponding to 50 mg total phospholipids per kg body weight) may be given at intervals of 12 to 24 hours. If the response to the initial dose is inadequate, a prompt second dose (30 to 60 minutes after initial administration) of 1.2 ml Alveofact per kg body weight (corresponding to 50 mg total phospholipids per kg body weight) is recommended.
- Thorough tracheal aspiration is required prior to each application in order to prevent impaired proliferation and foaming of Alveofact, caused by the mucosa.
    - If oxygenation is acutely deteriorated (rise in carbon dioxide partial pressure and drop in oxygen partial pressure) it is recommended to check the correct positioning and patency of the ventilation tube.
    - Over-acidity of the blood, caused by impaired meta bolism or gas exchange, should be corrected prior to administration of Alveofact, since preclinical findings suggest that the efficacy of the preparation can thereby be impaired.
- When using a double-lumen tube or "side port connector" to administer Alveofact without interrupting ventilation, the respiratory parameters must be adjusted with particular care.

Overdose of Alveofact

Overdose has not yet been reported. In the unlikely event of inadvertent overdose, it is recommended to aspirate the applied quantity of liquid applied as much as possible if there is a clinical deterioration. Symptomatic therapy should be given where necessary.

4. Possible side effects

Like all medicines, Alveofact can cause side effects, although not everybody gets them.

As a rule the following frequency figures form the basis for the evaluation of the mentioned side effects:

Very common	More than 1 treated patient out of 10
Common	1 to 1 0 treated patients out of 100
Uncommon	1 to 1 0 treated patients out of 1000
Rare	1 to 1 0 treated patients out of 10000
Very rare	Less than1 treated patients out of 10000
Not known	Frequency cannot be estimated from the available data

Which side effects may occur?

No substance-related side effects are to be expected when using as directed.

Due to the quantity of fluid, brief obstruction of the upper airways may occur immediately after application of Alveofact, which can be remedied by increasing the respiratory pressure for 30 to 60 seconds.

Caution:

There have been single reports of obstruction of the tracheal by viscous material. A causal connection to the use of Alveofact has not been proven.

Cerebral and pulmonary haemorrhage has been described. Their frequency correlates roughly to declarations in the literature for this patient population. It is unlikely that premature neonates are already sensitive (hypersensitivity) to protein from bovine lung, but such a condition may cause anaphylactoid reactions which require the usual emergency treatment.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Alveofact

Keep medicines out of the reach and sight of children! Do not use Alveofact after the expiry date which is stated on the carton, the label of the vial containing the powder and the label of the syringe containing the solvent after {exp. date:}. The expiry date refers to the last day of that month.

Storage conditions

Do not store the powder and the solvent above 30°C. In India we instruct our channel partners to store the product in a refrigerator and maintain less than 30°C.

Do not freeze the powder, the solvent or the reconstituted suspension.

Shelf life after reconstitution, dilution or first opening of the container

The reconstituted suspension can be kept for up to six hours attemperatures up to 25^{0}C or 24 hours at 2-8^{0}C (refrigerated). In

such a case the vial and pre-filled syringe, respectively, need to be lightly agitated once prior to use.

6. Further information

What Alveofact contains

The active substance is: Phospholipid fraction from bovine lung

1 vial contains: 50.76-60.00 mg phospholipid fraction from bovine lung (powder), equivalent to a content of 66 mol or 50 mg total phospholipids as freeze-dried powder.

The other ingredients are:

1 pre-filled syringe with 1.2 ml solvent contains: Sodium chloride, sodium hydrogen carbonate, water for injections.

What Alveofact looks like and contents of the pack

One pack of Alveofact contains: 1 vial of powder, 1 pre-filled syringe with 1 .2 ml solvent, 1 cannula, 1 vial adapter.

FREQUENTLY ASKED QUESTIONS

1. What is the importance of the SP-C, regarding that Survanta® has more SP-C than us? Is it relevant, could Survanta® people attack us regarding that point?

Survanta® is supplemented with Dipalmitoylphosphatidylcholine (DPPC), palmitic acid and triacylglycerol. Survanta® and Exosurf contain less or no hydrophobic surfactant proteins (SP-B and SP-C), in contrast to Alveofact® contains 5.2 ±0.6 of SP-B and 12.9 ±1.7 of SP-C and Curosurf contains 3.2 ±0.5 and 10.1 ±1.5 Micrograms/micromol respectively. Bernhart et al. showed that low concentrations or the absence of SP-B or SP-C lead to poor surface tension function. *(Bernhard, Mottaghian et al. 2000).* This was confirmed by Laemmli et al. *(Laemmli 1970)*. As rapid DPPC adsorption requires the integration and assistance of surfactant proteins, exogenous DPPC probably did not improve the surface tension function of Survanta® under the dynamic in vitro conditions represented by the pulsating bubble surfactometer. According to Bernhard et al. 2003, Survanta® and Exosurf® were not only less potent than Alveofact® or Curosurf®, but also displayed an impaired intrinsic activity.

These findings contrast to those of McMillan and colleagues, agreeing with recent data on the poor adsorption properties of DPPC or isolated phospholipid mixtures to gas-liquid interfaces in the absence of SP-B/C. On the basis of these findings, we speculate that the clinical response to exogenous Survanta® or Exosurf® seen in patients with respiratory distress syndrome is not predominantly due to the intrinsic surface activity of these therapeutics, but involves the contribution of other, endogenous, mechanisms such as those occurring during

reprocessing of surfactant phospholipids. *(McMillan, Singhal et al. 1998, Ingenito, Mark et al. 1999, Bernhard, Mottaghian et al. 2000)*

2. What is the importance of the SP-B/SP-C ratio, is it relevant? Or it is just a number to put in perspective the lack of SP-B in Survanta®. Is there a clinical relevance for the patient, in terms of the lack of SP-A and SP-D in Alveofact®?

SP-A and SP-D are hydrophilic, SP-C and SP-D are hydrophobic. As a result of the organic solvents and chromatographic methods used to concentrate and purify the lipophilic surfactant components, SP-A and SP-D are mostly lost during the manufacturing process. The highly hydrophobic surfactant proteins SP-B and SP-C remain. That applies for both, Curosurf® and Alveofact®. SP-B and SP-C are essential for the effectiveness of the preparations available on the market.(Perez-Gil and Keough 1998). None of the commercial surfactants contain SPA. *(Notter, Tabak et al. 1980, Orgeig, Barr et al. 1995, Bernhard, Mottaghian et al. 2000).*

According to the current state of knowledge SP-B plays a major role in the extracellular transportation of the lipids, the ratio is not relevant. Bernhard et al. conclude that unmodified lipid extract surfactants display an intrinsic activity comparable to that of native surfactant. However, their potency is impaired compared with native surfactants, likely because of the absence of SP-A and a reduced concentration of SP-B/C. Semisynthetic (Survanta®) or synthetic (Exosurf®) surfactants were unable to demonstrate surface tension properties comparable to those of native or lipid extract surfactants, such as Alveofact®.

3. What are the most relevant differences between Survanta® and Alveofact®?

Animal based natural surfactant obtained from lung and amnion or synthetic surfactant preparartions prepared under laboratory conditions are available on the market. According to the results of a comprehensive research carried out, natural surfactant preparations have been shown to be more advantageous than synthetic ones with respect to benefits and complications (Soll 2000). However, unlike molecular and experimental studies on the use of different natural surfactant preparations, there are only a few studies investigating the differences among clinical response. *(Speer, Gefeller et al. 1995, Bloom, Kattwinkel et al. 1997, Herting, Rauprich et al. 2001, Yalaz, Arslanoglu et al. 2004).* Also see answer in question 1 and 2. Further relevant differences are that Alveofact® is not a cold chain product and it's shelf life is 36 months. See answer to question Nr. 8. Even the administration of smaller volumes of Alveofact® than Survanta® is worth mentioning. Having in mind that the lungs of e.g. a 1000 g baby have a tidal volume of about 5 ml it can easily be understood that the application of 4 ml is a considerable volume load.

Clinical data suggest that the two products are comparable. **Yalaz et al. 2004** compared Alveofact® and Survanta® in terms of effectiveness and side-effects. A total of 50 infants (<36 weeks gestation) with RDS were randomly treated with Alveofact (N=25) or Survanta (N=25). Alveofact was administered at 50 mg/kg/dose whereas one dose of Survanta contained 100 mg/kg. The dose of each surfactant preparation was repeated up to two more times, between 6 – 24 hours as required by blood gas and chest X-ray findings. The respiratory status as determined by mean FiO2, MAP (mean airway pressure) and a/APO2 (arterial/alveolar oxygen tension ratio), was significantly

improved for the Alveofact treatment group at the 2nd hour but had disappeared by the 6th hour. This study did not fully confirm the results of the Baroutis et al. study but there is one major difference between these two studies,which concerns the treatment dosage: In the Yalaz-study, the infants were treated with 100 mg/kg/dose of Survanta but with only 50 mg/kg/dose of Alveofact. Infants received up to three doses (resulting in maximum surfactant quantities of 300mg (Survanta) and 150mg (Alveofact) respectively).

Baroutis et al. also administered 100 mg/kg/dose of Survanta, but they administered twice the Alveofact dose compared to the Yalaz - study, namely 100 mg/kg/dose. In total, four doses were allowed according to the study protocol (maximum amounts for both surfactant preparations was 400 mg). This treatment regimen is exactly what is recommended by the current guideline particularly concerning the initial dose. It may be assumed that the differences in outcome between the Baroutis et al. and Yalaz et al. studies can be explained by the different treatment doses and therefore the total amounts administered. The publication of **Seeger et al.** may furthermore be of interest in this context. They examined the inhibition profiles of Alveofact, Survanta (and of Curosurf and calf lung surfactant extract (CLSE)) towards fibrinogen, albumin and haemoglobin using the pulsating bubble surfactometer.. Survanta (and Curosurf) were dose-dependently inhibited by fibrinogen > haemoglobin > albumin. In contrast, Alveofact (and CLSE) were only moderately inhibited by fibrinogen and were not affected by haemoglobin and albumin up to protein-surfactant ratios of 2:1. The authors conclude that “differences in phospholipid profiles and hydrophobic apoprotein contents (e.g. low SP-B quantities in Curosurf and Survanta, high quantities in CLSE and Alveofact) may underpin these findings. Such differences may be relevant for surfactant function under conditions of increased alveolar protein load” (e.g. ARDS).

20 Based on the results of these two clinical trials it can be summarized that Alveofact proved to be superior to Survanta when applicated in the same dose (100 mg/kg) and equivalent when administered in half of the dose of Survanta (50mg/kg vs 100 mg/kg). This advantage in favour of Alveovact is probably explained by the differences in the composition of both surfactant preparations. *(Soll 2000, Yalaz, Arslanoglu et al. 2004).*

4. What are the advantages and/or disadvantages that Survanta® has regarding the three added synthetic phospholipids on the product?

See also answer to question 1. In contrast to Alveofact®, Survanta® is supplemented with synthetic Dipalmitoylphosphatidylcholine (DPPC), Glyceroltripalmitate and Palmitic acid. Survanta® has higher levels of non-phosphatidylcholine phospholipids such as sphingomyelins and phosphatidylethanolamines and these phospholipids limit the lowest surface tension attainable in bovine surfactant preparations. Despite their enrichment in DPPC Survanta® and Exosurf® exhibited poor surface activity because of low or absent SP-B/C (Bernhard, Mottaghian et al. 2000). Seeger et al. examined the inhibition profiles of Alveofact®, Survanta® (and of Curosurf® and calf lung surfactant extract (CLSE)) towards fibrinogen, albumin and haemoglobin using the pulsating bubble surfactometer.. Survanta® and Curosurf® were dose-dependently inhibited by fibrinogen > haemoglobin > albumin. In contrast, Alveofact® (and CLSE) were only moderately inhibited by fibrinogen and were not affected by haemoglobin and albumin up to protein-surfactant ratios of 2:1.In contrast, Alveofact® (and CLSE) were only moderately inhibited by fibrinogen and were not affected by haemoglobin and albumin up to protein-surfactant ratios of 2:1.

The authors conclude that “differences in phospholipid profiles and hydrophobic apoprotein contents (e.g. low SP-B quantities in Curosurf® and Survanta®, high quantities in CLSE and Alveofact®) may underpin these findings. Such differences may be relevant for surfactant function under conditions of increased alveolar protein load” (e.g. ARDS). There is a step in the Survanta® manufacturing process that removes cholesterol, “but it also removes the surfactant apoprotein B, the apoprotein most critical for full biophysical activity. *(Mizuno, Ikegami et al. 1995, Wang, Gurel et al. 1996)*

5. In terms of the method of administration of the product, what are the main differences between Alveofact® and Survanta®?

In contrast to Survanta® the SPC of Alveofact® does not not recommend a certain method of administration, it is administered intratracheally. According to the German Guideline it is suggested to use surfactant only in a preventive manner (within the first hour after birth) in preterm infants <27 gestational weeks and preterm infants without antenatal corticosteroids. Furthermore, it is recommended to use the INSURE (Intubation, Surfactant, Extubation) method and subsequent switch to CPAP *(Rojas-Reyes, Morley et al. 2012)*. In spontaneously breathing infants receiving CPAP the use of LISA (Less Invasive Surfactant Administration) is recommended. The guideline recommends the interventional treatment (rescue treatment) particularly in preterm infants 27-32 gestational weeks with clinical or radiological signs *(Gortner 2017)*.

6. In case the neonatologist decides to store the reconstituted suspension at 2-8^{0}C for 24 hrs, what is the correct method of administration on this case?

For the security of patients and consumers many protein temperature-sensitive products require that they be maintained at a constant temperature. Alveofact® is not a cold chain product. Its shelf life is 36 months without refrigeration. If Alveofact® is kept at 2°-8°C, it should be warmed before administration by standing at room temperature for at least 20 minutes or warmed in the hand for at least eight minutes. Before use, the vial should be gently turned upside-down, in order to obtain a uniform suspension. Do not shake and do not heat it up. There are 2 different methods for reconstruction of the powder: with vial adapter or with cannula. Once opened, the suspension is stable for 6 hours at 25°C or 24 hours at 2-8°C.

7. What is the Dosage, Bioavailability & Bioequivalence of Alveofact vs Curosurf & Survanta?

The surfactant pool is assumed **100 mg/kg body weight in full term neonates** (Glatz, Ikegami et al. 1982, Jacobs, Jobe et al. 1982) and **1-15 mg/kg body weight in a preterm infant with NRDS** (Hallman, Merritt et al. 1986, Bohlin, Merchak et al. 2003). The conventional dose of surfactant, therefore, is 100 mg/kg of phospholipids (Johansson and Herting 2004).

	Alveofact	Survanta	Curosurf
Dosage mg/kg	50-100	100	100-200
Volume ml/kg	1.2-2.4	4	1.25-2.5

Therapeutic administration of surfactant at a dose of 200 mg/kg offers no advantages *(Halliday, Tarnow-Mordi et al. 1993).* Such a dosage is used in Europe in some European intensive care units, suggesting, that the decision to use a high surfactant dose is mainly based on the recommendations made by the manufacturer *(van Kaam, De Jaegere et al. 2011).*

Bioavailability / Bioequivalence: Since **Alveofact** is active locally in the lung, it does not enter the blood circulation. It has **no effect** on the bioavailability/bioequivalence.

8. What are the Hemodynamic effects of Alveofact?

The same applies to hemodynamic effects (see above: Dosage, Bioavailability & Bioequivalence)

9. Alveofact: Effectiveness in MAS (Meconium Aspiration Syndrome), can it be used in MAS?

Experimental data, animal studies and randomized clinical trials have **all demonstrated the efficacy of surfactant substitution in MAS** (Soll and Dargaville 2000, Engle, American Academy of Pediatrics Committee on et al. 2008). A more recent meta-analysis revealed no significant reduction in mortality, but **the risk of ECMO (= extracorporeal membrane oxygenation treatment) was reduced by one third, that means the course of the illness was improved by surfactant application.** There were no differences in terms of the risk of other complications, including pneumothorax and BPD *(El Shahed, Dargaville et al. 2007)*.

Higher and repeat doses of surfactant (cumulative doses 300–600 mg/kg body weight) are necessary in MAS, and the onset of effect is often protracted. Although bronchoalveolar lavage (BAL) with diluted surfactant in MAS patients appears to reduce the severity of

pulmonary damage and the course of the disease (Lam and Yeung 1999, Wiswell, Knight et al. 2002) considerable reservations regarding the safety of the BAL procedure have prevented a wider acceptance of this method *(Kattwinkel 2002).*

10. What are references of Alveofact safety on Bovine Spongiform Encephalopathy (BSE) ?

Due to its bovine origin, a theoretical risk of Alveofact transmitting pathogens of bovine spongiform encephalopathy cannot be excluded from the outset. In accordance with national and EU guidelines, the following procedure is applied for the extraction of bronchoalveolar lavage fluid (BALF) during the manufacture of Alveofact: Only lungs are taken from animals that have never been fed with meat and bone meal or feed containing meat and bone meal or tallow. The cattle are slaughtered only at EU-certified abattoirs. Only cattle are used that originate from the Federal Republic of Germany and from stock that is not subject to any prohibitory animal disease legislation. The animals undergo veterinary examination prior to slaughter. Only those animals assessed as healthy are used for the extraction of bronchoalveolar lavage fluid. Slaughtering procedures ensure that the lung does not come into contact with the brain and/or bone marrow. The lungs harvested under such precautionary methods are lavaged immediately after slaughter. The extracted lavage fluids are pooled.

Testing for BSE and viral safety: A brain sample is taken from each cattle and tested immediately after slaughter in an approved laboratory using a certified BSE quick-test. Should the test prove positive in one or more animals, the entire BAL pool is discarded and destroyed. Along with BSE testing, the BAL pool is tested for viral contamination. Tests are carried out for enveloped and non-enveloped DNA and RNA viruses. Moreover, a test for bovine

leucosis antibodies is performed. Only BAL pools which prove to be free of viruses and have no antibodies against bovine leucosis are accepted for further processing. The high degree of safety achieved by such measures regarding the transmission of BSE pathogens is raised considerably by the further manufacturing process to which the BAL pool is subjected. The reduction/inactivation efficacy of the manufacturing process was examined in cooperation with the University of Amsterdam and the Institute for Biochemistry in Ivera (Italy) using experimentally infected starting material *(Werz, Berthold et al. 1994, Werz, Hoffmann et al. 1997)*.

Based on the findings, the competent German authority (Federal Institute for Drugs and Medical Devices, BfArM) has attested the safety of Alveofact with regard to the transmission of pathogens (prions) of bovine spongiform encephalopathy. The European Directorate for the Quality of Medicines (EDQM; now known as EDQM & HealthCare) has also confirmed, after reviewing the provided documents, that the pulmonary surfactant (Alveofact) fulfils the criteria defined in the latest version of the monograph, 'Products with risk of transmitting agents of animal spongiform encephalopathies No. 1483 of the European Pharmacopoeia and issued Alveofact the Certificate of Suitability No. R1-CEP 2000-305-Rev 00 (pulmonary surfactant).

11. What is the impact on gas exchange of high dose has significant as compared to low dose as per Gortner 1995 and many other studies. Then why Alveofact is low dose since it would increase need for more dosages after 6-8 hrs ?

The extracellular alveolar surfactant pool (measured as DSPC = desaturated phosphatidylcholine) amounts approx. 100 mg/kg body weight at the birth of a full-term neonate, and 1-15 mg/kg

body weight in a preterm infant with NRDS. The minimum surfactant dose required to coat the alveolar surface with a surfactant film is calculated with 2-10 mg/kg body weight. (*Chu, Clements et al. 1967, Hallman, Merritt et al. 1986, Obladen and Segerer 1991)*. Dosage: Manufacturers **recommend initial doses of between 50 and 200 mg/kg body weight** in the respective package leaflet. Controlled clinical trials have been performed to compare 50 versus 100 mg/kg body weight of a bovine surfactant (bovactant) and 100 versus 200 mg/kg body weight of a porcine surfactant (poractant alfa) in preterm infants with RDS *(Halliday, Tarnow-Mordi et al. 1993, Gortner, Pohlandt et al. 1994).* In terms of gas exchange, the dose of 100 mg/kg BW was superior to 50 mg/kg of the bovine surfactant *(Gortner, Pohlandt et al. 1994).*

Advantage over the dose of 100 mg/kg body weight *(Halliday, Tarnow-Mordi et al. 1993)*. In this trial a **low dose surfactant regimen was found to be as effective as a high dose regimen to treat babies with severe respiratory distress syndrome.** For Curosurf an average total dose of 242 mg/kg was as good as 380 mg/kg, and was probably enough to replace the total pool of surfactant phospholipids in the neonatal lung *(Jobe and Ikegami 1987)* and to overcome inactivation or inhibition by other proteins leaking into the airways *(Fuchimukai, Fujiwara et al. 1987)*. This dose is about 80 times that of the estimated amount of phospholipids needed to form an alveolar monolayer *(Marks, Notter et al. 1983)*. **This may explain why the higher dosage achieved no further benefit** *(Halliday, Tarnow-Mordi et al. 1993)*. Halliday et al. concluded, that only one of all 18 comparisons of clinical outcome, the number of days receiving > 40% oxygen, significantly favored the high dose group and then only weakly (p<005). As no adjustment was made to allow for the large number of comparisons performed, this isolated

secondary result should be interpreted with caution. There were dose-dependent effects of surfactant on oxygenation with blood gas measurements favoring the high dose group during the first 36 hours after treatment. These early benefits of high dose treatment were not reflected in improved long term outcome, although fewer babies needed retreatment compared with the low dose group. As an initial dose, therefore, 100 mg/kg BW surfactant is currently recommended for treatment of uncomplicated RDS.

12. Why Alveofact is low dose since increases the need for more dosages after every 6-8 hrs?

In case of an inspiratory oxygen requirement of > 30%-60% repeat administration should take place 6-8 hours at the earliest after the initial dose of surfactant. Given the variable patterns, it is not appropriate in this case to specify a fixed regimen *(Sweet, Bevilacqua et al. 2007, AWMF-Guidelines-Register: 2017)*. The doses investigated with respect to repeat application ranged from 50 to 100 mg/kg body weight. Up to three repeat doses were administered in most studies. In a European multicenter study, improved gas exchange and reduced mortality were demonstrated in preterm infants receiving multiple doses!!! *(Speer, Robertson et al. 1992).*

13. How low dose of Alveofact (1.2) is equivalent to high dose of Survanta (4 mL/kg) of BW in effectiveness ?

Having in mind that the lungs of e.g. a 1.000 g baby have a tidal volume of about 5 ml it can easily be understood that the application of 4 ml is a considerable volume load. Clinical data suggest that the two products are comparable. Yalaz et al. 2004 compared Alveofact® and Survanta® in terms of effectiveness and sideeffects. A total of 50 infants (<36 weeks gestation) with RDS were randomly treated

with Alveofact (N=25) or Survanta (N=25). Alveofact was administered at 50 mg/kg/dose whereas one dose of Survanta contained 100 mg/kg. The dose of each surfactant preparation was repeated up to two more times, between 6 – 24 hours as required by blood gas and chest X-ray findings.

The respiratory status as determined by mean FiO2 (Fraction of inspired oxygen), MAP (mean airway pressure) and a/APO2 (arterial/ alveolar oxygen tension ratio), was significantly improved for the Alveofact treatment group at the 2nd hour but had disappeared by the 6th hour. **The study shows no significant differences and confirms that the dose of Alveofact 50 mg / kg body weight is as effective as the higher Survanta dose. Having a fixed per-mg price in India, the lower Alveofact dosage is very lucrative and, from an economic point of view, very appealing.**

This study did not fully confirm the results of the Baroutis et al. study but there is one major difference between these two studies, which concerns the treatment dosage: **In the Yalaz-study, the infants were treated with 100 mg/kg/dose of Survanta but with only 50 mg/kg/ dose of Alveofact. Infants received up to three doses (resulting in maximum surfactant quantities of 300 mg (Survanta) and 150 mg (Alveofact) respectively.**

Baroutis et al. also administered 100 mg/kg/dose of Survanta, but they administered twice the Alveofact dose compared to the Yalaz-study, namely 100 mg/kg/dose. In total, four doses were allowed according to the study protocol (maximum amounts for both surfactant preparations was 400 mg). This treatment regimen is exactly what is recommended by the current guideline particularly concerning the initial dose. It may be assumed that the differences in outcome between the Baroutis et al. and Yalaz et al. studies can be explained

by the different treatment doses and therefore the total amounts administered. *(Baroutis, Kaleyias et al. 2003)*

The publication of Seeger et al. may furthermore be of interest in this context. They examined the inhibition profiles of Alveofact, Survanta (and of Curosurf and calf lung surfactant extract (CLSE)) towards fibrinogen, albumin and haemoglobin using the pulsating bubble surfactometer. Survanta (and Curosurf) were dose-dependently inhibited by fibrinogen > haemoglobin > albumin. In contrast, Alveofact (and CLSE) were only moderately inhibited by fibrinogen and were not affected by haemoglobin and albumin up to protein-surfactant ratios of 2:1.

The authors conclude that “differences in phospholipid profiles and hydrophobic apoprotein contents (e.g. low SP-B quantities in Curosurf and Survanta, high quantities in CLSE and Alveofact) may underpin these findings. Such differences may be relevant for surfactant function under conditions of increased alveolar protein load” (e.g. ARDS). **Based on the results of these two clinical trials it can be summarized that Alveofact proved to be superior to Survanta when applicated in the same dose (100 mg/kg) and equivalent when administered in half of the dose of Survanta (50mg/kg vs 100 mg/kg).** This advantage in favor of Alveovact is probably explained by the differences in the composition of both surfactant preparations. *(Soll 2000, Yalaz, Arslanoglu et al. 2004).*

14. What is LISA vs MIST therapy, which one's better? Where does Alveofact fit in?

	Conventional	Insure	Lisa	Mist
Mechanical ventilation	Yes, continuously	Yes, briefly during intubation	No	No
Spontaneous breathing maintained	No	Yes, prior to intubation, surfactant instilation and after extubating	Yes	Yes
Continuous positive airway pressure (CPAP)	No	Yes, prior to intubation, surfactant instilation and after extubating	Yes, continuously	Yes, continuously
Surfactant application	e.g. through a neonatal/ pediatric tracheal tube fitted with a side port	e.g. through a neonatat/ pediatric tracheal tube fitted with a side port	Fine flexible catheter	Rigid thin vascular catheter

Two similar methods of administering surfactant via a fine catheter without 'traditional' intubation have been studied. The first, developed in Germany and now used widely in parts of Europe, **uses a fine flexible catheter positioned in the trachea whilst the baby is kept on CPAP,** using laryngoscopy and Magill's forceps (*Gopel, Kribs et al. 2011),* also known as **LISA** (less invasive surfactant administration). The second, developed in Australia, uses a more rigid thin vascular catheter that is stiff enough to be positioned in the trachea under

direct laryngoscopy without forceps whilst the baby is kept on CPAP *(Dargaville, Aiyappan et al. 2013),* also known as **MIST** (minimally invasive surfactant treatment). With both methods the aim is to maintain spontaneous breathing on CPAP whilst surfactant is gradually administered over several minutes using a syringe without resorting to routine bagging. Both of these methods have been compared to traditional intubation for surfactant administration followed by mechanical ventilation. Large cohort studies from the German neonatal network with experience of this method were encouraging, reporting reduced use of mechanical ventilation and less BPD *(Gopel, Kribs et al. 2015).*

A randomized non-blinded clinical trial of extremely preterm infants between 23 and 27 weeks' gestation showed no significant increase in survival without BPD in those treated with LISA although these infants required less ventilation, had fewer pneumothoraces and a reduction in severe intraventricular haemorrhage. However, nearly 75% of the intervention group eventually needed MV, and the rate of desaturations was significantly higher in this group *(Kribs, Roll et al. 2015)*. Although direct comparison with INSURE (Intubate-Surfactant-Extubate) reported improved outcomes in one study *(Kanmaz, Erdeve et al. 2013)*, reanalysis of the data could not reproduce statistical significance when included in a meta-analysis, and therefore to date this is still uncertain *(More, Sakhuja et al. 2014)*

KEY DIFFERENTIATORS

	Parameter	Alveofact	Survanta	Curosurf	Neosurf
1.	**Source**	Bovine Lungs/ Lavage	Bovine Lungs/ Minced	Porcine Lungs/ Minced	Bovine Lungs/ Lavage
2.	**Dose per kg**	50 mg	100 mg	200 mg	100 mg
3.	**Volume per kg**	1.2 ml	4 ml	1.5 ml	3 ml
4.	**Available SKUs**	1.2 ml	4 ml & 8 ml	1.5 ml & 3 ml	3 ml & 5 ml
5.	**Active phospholipid concentration per ml**	45 mg	25 mg	80 mg	27 mg
6	**Cost for Initial Treatment**	7030	13178	12280	8897
7.	**Warming required**	Not required upto 30^0C	Yes	Yes	Yes
8.	**Vial Wastage**	Nil	Yes	Yes	Yes
9.	**Storage temperature**	Upto 30^0C Still keep in fridge considering Indian temperature conditions	2-8^0C Ampoule	2-8^0C Ampoule	2-8^0C Ampoule
10.	**Phospholipid %**	90% phospholipid	84% phospholipids	99% phospholipids	DPPC (40%)

	Parameter	Alveofact	Survanta	Curosurf	Neosurf
11.	**Presence of supplemental lipids**	1% hydrophobic proteins + 3% cholesterol + 0.5% FFA & other components such as triglycerides	1% hydrophobic proteins + 6% FFA mixed with palmitic acid & tripalmitin to standardize compositions	1% hydrophobic surfactant proteins	10% proteins, 50% cholesterol
12.	**Viscosity**	8 times less viscous	High	High	8 times less viscous
13.	**SP B protein concentration** [1&2]	SP B: 5.2 ± 0.6 SP C: 12.9 ± 1.7	SP B:1.3 ± 0.2 SP C: 16.5 ± 3.7	SP B: 3.2 ± 0.5 SP C: 10.1 ± 1.5	Not defined
14.	**Stability**	36 months	15 months	15months	36 months
15.	**Mode of application**	Bolus	Bolus or 4 partial boli in 4 different positions	Bolus or 2 partial boli left/right	Bolus
16.	**Loss of activity through plasma proteins**	Low	High	High	Low
17.	**Galenics**	Lyophilized	Vesicle dispersion	Vesicle dispersion	Vesicle dispersion
18.	**Infants requiring one dose only**[3]	78.10%	51%	73%	
19.	**Incidence of Necrotising Enterocolitis**[3]	1.20%	NA	10.50%	NA

Planned Communication is an essence

Early Prophylactic vs Late Selective Surfactant treatment

P Problem

Doctor, delay in surfactant therapy increases the risk of lung injury among premature neonates showing symptoms of early RDS.

A Acknowledgement

Dr you will agree that this challenge needs to be managed.

W Wants

Early or prophylactic surfactant has been shown to be effective in reducing mortality and morbidity.

N Needs

There is a need for improved therapy which can help reduce RDS complications and prevent lungs from collapsing.

Planned Communication is an essence

Introducing Alveofact

F Features

Alveofact, Brand from Germany which has following features -

- Freeze dried powder which can be stored at 30^0C.
- No warming required
- Contains highest concentration of SP-B. proteins[1&2].
- Purity due to lavage, contains 90% phospholipids. More the phospholipids more the surface tension No supplemental lipids added to lavage.
- Low viscosity.
- High clinical efficacy[2].

A Advantage

- Fewer days of oxygen administration and fewer air leakage[2]
- Significant reductions in the incidence of pneumothorax.
- Significant improvement in survival.
- Decreases risk of bronchopulmonary dysplasia[7]
- Decreased risk of chronic lung disease with early use[7].

B Benefits

- Better clinical outcome of premature newborns
- Effective in improving the immediate need for respiratory support.
- Decreased need for mechanical ventilation.
- Increased survival rate.
- Marked improvement in compliance of lungs and oxygenation may occur within minutes.

Source: [1]Bernhard 2000, Commercial versus Native Surfactants, [2]Yalaz 2004, Efficiency Alveofact vs Survanta. [7]Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2000

Planned Communication is an essence

against Survanta & Curosurf, SP B protein concentration

P Problem

Dr as you are well aware, SP B deficiency is one of the cause of fatal neonatal respiratory disease.

A Acknowledgement

You will agree with me is to have alternative NRDS therapy which offers high SP-B content.

W Wants

SP B and phosphotidylcholine are the major phospholipid found in surfactant and is responsible for decreasing the surface tension at the air-water interface in the alveoli. SP B is essential for surfactant's surface tension lowering properties.

N Needs

In the light of above discussion, Dr there is a need for a surfactant with higher SP B concentration.

Planned Communication is an essence

Introducing Alveofact

F Features

Alveofact, Brand from Germany which has following features -

- Contains highest concentration of SP-B proteins[1&2].
- Purity due to lavage, contains 90% phospholipids with better more the phospholipids more the surface tension.
- High clinical efficacy[2].
- Freeze dried powder which can be stored at 30^0C.

A Advantage

- Fewer days of oxygen administration and fewer air leakage[5].
- Fewer days on ventilator.
- Low viscosity.
- Stability data for 3 years
- Fewer cases of Necrotizing enterocolitis and hemorrhage.

B Benefits

- Decreased need for mechanical ventilation
- Increased survival rate.
- Marked improvement in compliance of lungs and oxygenation may occur within minutes.

Source: [5]Baroutis et al Eur J Ped 2003

Planned Communication is an essence

against competition, NCPAP support

P Problem

As you are well aware that the use of early nCPAP can avoid mechanical ventilation in many VLBW-infants with RDS. Surfactant administration alongwith NCPAP provide better results.

A Acknowledgement

Dr I am sure you will agree with me.

W Wants

A surfactant which is NCPAP supported and has less side effects.

N Needs

NCPAP alongwith surfactant is highly effective in management of NRDS.

Planned Communication is an essence

Introducing Alveofact

F Features

Alveofact, Brand from Germany which has following features -

- NCPAP support was needed for 43 patients as compared to 51 Survanta & 48 Curosurf[4].
- Contains highest concentration of SP-B proteins[1&2].
- Purity due to lavage, contains 90% phospholipids. More the phospholipids more the surface tension.
- Freeze dried powder which can be stored at 30^0C.

A Advantage

- Improved oxygenation and reduced barotrauma.
- Fewer days on ventilator so less monitoring required.
- Cost-effective Stability data for 3 years.
- Fewer cases of Necrotizing enterocolitis and hemorrhage[3&6].

B Benefits

- Decreased need for mechanical ventilation
- Increased survival rate.
- Decreased deaths due to RDS.
- Marked improvement in compliance of lungs and oxygenation may occur within minutes.

Source: [3]Proquitte H al (Eur Respir J 1993), Ramanathan et al (Am Perinatal J, 2004) [6]Kribs, Gopel et al 2015, Acta Pediat 104: 241-246

Surfactant inhibition by plasma proteins: differential sensitivity of various surfactant preparations

W. Seeger, C. Grube*, A. Gunther, R. Schmidt

Surfactant inhibition by plasma proteins: differential sensitivity of various surfactant preparations. W. Seeger, C. Grube, A. Gunther, R. Schmidt. @ERS Journals Ltd 1993.

ABSTRACT: Leakage of plasma proteins into the alveolar space may inhibit surfactant function. We compared the surface properties and the sensitivity to inhibitory proteins of different organic solvent surfactant extracts and a synthetic surfactant.

Experiments were performed in the pulsating bubble surfactometer, with surfactant concentrations ranging between 0.1 and 2 mg•ml4. Inhibition profiles to-wards fibrinogen, albumin and haemoglobin were obtained from calf lung surfactant extracts (CLSE), Alveofact, Curosurf and Survanta (all used in clinical replacement studies in respiratory distress syndrome (RDS) and of an apoprotein-based synthetic phospholipid mixture (PLM-C/II; DPPC:PG:PA=68.5:22.5:9, supplemented with 2% wt/wt non-palmitoylated human recombinant SP-C and 1% t/wt natural bovine SP-B).

In the absence of inhibitory proteins, all surfactants exhibited dose-dependent rapid adsorption (rank order of relative efficacy PLM-C/B = CLSE > Alveofact > Curosurf > Survanta). Minimal surface tension was reduced to near' zero values under dynamic compression (rank order PLM-C/B > CLSE > Alveofact = Curosurf) and to =4 mN.m4 (Survanta). Curosurf and Survanta were dose-dependentlly inhibited by fibrinogen > haemoglobin > albumin, with far-reaching loss of surface activity at protein-surfactant ratios above 1:1. In contrast, CLSE and Alveofact were only moderately inhibited by fibrinogen, and were not affected by haemoglobin and albumin,

up to protein-surfactant ratios of 2:1. PLM-C/B exhibited resistance to fibrinogen, intermediate sensitivity to albumin, and was severely inhibited by haemoglobin.

We conclude that various natural surfactant extracts and an apoprotein-based synthetic surfactant mixture markedly differ in their sensitivity to inhibitory plasma proteins. Differences in phospholipid profiles and hydrophobic apoprotein contents (e.g. low SP-B quantities in Curosurf and Survanta, high quantities in CLSE and Alveofact) may underlie these findings. Such differences may be relevant for surfactant function under conditions of increased alveolar protein load. *Eur Respir J., 1993, 6, 971-977.*

Commercial versus Native Surfactants

Surface Activity, Molecular Components, and the Effect of Calcium

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ABSTRACT: Despite their broad clinical use, there is no standardized comparative study on the functional, biochemical, and morphologic differences of the various commercial surfactants in relation to native surfactant. We investigated these parameters in Alveofact, Curosurf, Exosurf, and Survanta, and compared them with native bovine (NBS) and porcine (NPS) surfactant. For Curosurf and Alveofact the concentrations necessary for minimal surface tensions <5 mN/m were six to 12 times higher (1.5 and 3 mg/ml, respectively) than with NPS and NBS. Exosurf and Survanta only reached 22 and

8 mN/m, respectively. Increasing calcium to nonphysiologic concentrations artificially improved the function of Alveofact and Curosurf, but it had little effect on Exosurf and Survanta. Impaired surface activity of commercial versus native surfactants corresponded with their lack in surfactant protein SP-A and decreased SP-B/C. The higher surface activity of Curosurf compared with Alveofact corresponded with its higher concentration of dipalmitoylphosphatidylcholine (DPPC). Despite their enrichment in DPPC Survanta and Exosurf exhibited poor surface activity because of low or absent SP-B/C. Ultrastructurally, Curosurf and Alveofact consisted mainly of lamellar and vesicular structures, which were also present in NPS and NBS. Exosurf contained crystalline structures only, whereas the DPPC-enriched Survanta contained separate lamellar/vesicular and crystalline structures. We conclude that *in vitro* surface activity of commercial surfactants is impaired compared with native surfactants at physiologic calcium concentrations. In the presence of SP-B/C, surface activity corresponds to the concentration of DPPC. Our data underscore the importance of a standardized protocol at physiologic calcium concentrations for the *in vitro* assessment of commercial surfactants.

Comparison of three treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome

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ABSTRACT: The aim of the study was to compare the treatment regimen of three natural surfactants of different extraction and formulation (Alveofact [Surfactant A = SA], Poractant [Surfactant B = SB] and Beractant [Surfactant C = SC]) in neonatal respiratory distress syndrome (RDS). Premature infants of ≤32 weeks' gestation with birth weight of ≤2,000 g and with established RDS requiring artificial ventilation with a FiO2 ≥0.3 were randomly assigned to receive at least two doses of SA, SB or SC (100 mg/kg per dose). Infants who remained dependent on artificial ventilation with a FiO2 ≥0.3 received up to two additional doses. There were no differences among the groups regarding the necessity for more than two doses. The SA and the SB groups spent fewer days on a ventilator (p-value SA/SB 0.7, SA/SC 0.05, SB/SC 0.043) compared with the SC group, needed fewer days of oxygen administration (p-value SA/SB 0.14, SA/SC 0.05, SB/SC 0.04) and spent fewer days in hospital (*p*-value SA/SB 0.65, SA/SC 0.04, SB/SC 0.027). There were no statistically significant differences in the incidence of mortality, chronic lung disease, air leaks, necrotising enterocolitis, retinopathy of prematurity and intraventricular haemorrhage among the three groups.

Conclusion: The Alveofact and Poractant groups spent fewer days on the ventilator, needed fewer days of oxygen administration and spent fewer days in hospital compared with the Beractant group but no differences were observed among the three groups with regards to mortality and morbidity.

A Comparison of Efficacy Between Two Natural Exogenous Surfactant Preparations in Premature Infants with Respiratory Distress Syndrome

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Vergleich der Wirkung zweier natirlicher Surfactantpraparate in der Therapie des Atemnotsyndroms Frihgeborener

ABSTRACT: The mortality and various morbidity rates have been substantially reduced by means of exogenous surfactant replacement, the cornerstone in the treatment of respiratory distress syndrome (RDS) in premature infants.

The objective of this study is to compare two natural surfactant preparations (Alveofact®, Survanta®) in terms of effectiveness and side-effects.

A total of 50 infants with RDS were given surfactant due to RDS were taken into the scope of this study. Survanta® and Alveofact® were administered to randomized infants with RDS and the results obtained during clinical observations were compared. Second hour mean $Fi0_2$, MAP and $a/AP0_2$ values showed changes in favour of Alveofact® (n=25) group compared to the Survanta® (n=25) group ($p < 0.05$ for each parameter). However, this difference disappeared in the 6th hour. No statistical difference was established between the two groups with regard to side-effects (pneumothorax, sepsis, intraventricular hemorrhage, bronchopulmonary dysplasia), duration of mechanical ventilation in survivors, duration of hospitalization in survivors and mortality before the 28th day.

It was concluded that results obtained with different surfactant preparations having dissimilar compositions were not different in terms of final impacts and side-effects.

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