Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (19):115-121
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Characteristics of performance of surfactant therapy in patients with bronchiectatic disease

Pavel I. Korg[2], Vitaliy V. Makarov[1], Anna O. Syrovaya[1], Vladimir A. Makarov[1], Yuliya V. Ivanova[2] and Tatyana S. Tishakova[1]

[1]Kharkiv National Medical University, Kharkiv, 61022, Kharkiv, 4 Nauky Avenue, Ukraine
[2]V.T. Zaytsev Institute of General and Emergency Surgery of NAMS of Ukraine, 61018, Kharkiv, 1 Balakireva vyezd, Ukraine

---

ABSTRACT

Application of surfactant therapy in patients with bronchiectasis induces normalization of phospholipids concentration in the condensate of inspiratory air, normalization of cytological changes in sputum *and improvement of physical properties of sputum. This research supports efficiency of inhalation route of administration of surfactant preparations in respiratory distress syndrome, pulmonary tuberculosis.*

Key words: bronchiectatic disease, surfactant therapy.

INTRODUCTION

In recent years, there is a growing number of patients with bronchiectatic disease (BED) [1, 6]. Bronchiectasises among others pulmonary diseases among adults range from 10% to 20% [2].

In last years, there is a growing number of articles devoted to the studying of surfactant at the inflammatory lung diseases [3, 9, 13, 15, 18].

Study data have been shown that state of surfactant system of the lungs at chronic inflammation dislocates structural organization of the lungs and causes dislocations in surfactant system, intensity of which depends on the damage level of alveolar parenchyma. Abnormalities in pulmonary surfactant system at chronic inflammation are caused by the duration of causative agent's persistence factor and also by the adverse effect of long and intensive antibacterial therapy regimens [4, 5, 11].

Peculiarities of studying an intracellular surfactant secretion in chronic inflammation and long-course antibacterial therapy are of practical importance in terms of correctability [4, 7].

Surfactant preparations began to be applied in the treatment and phrophylaxis of respiratory distress syndrome (RDS) since 80-thy years of last century after obtaining of exogenic surfactant. In the works of foreign authors it was found that in RDS expressed disorders of surface-active properties of surfactant occur [14, 16, 17]. Soon after it was shown that main component of surfactant is dipalmitoylphosphatidylcholine (DPPFCH) and researches from different countries became undertake attempts to use surfactant for treatment and prophylaxis of RDS [10, 13, 17]. Researchers observed changes in respiratory mechanism during the studies of mechanism of action of exogenously administered surfactant. Spontaneous breathing in animals with surfactant deficiency is accompanied by the increasing of expiratory volume, lungs instability by the time of expiration completion and almost full defervescence. In contrary, after administration of surfactant lungs of premature animals keep enough volume by the moment of expiration. Epithelial damage in lungs with surfactant deficiency is a result of repeating forced

inspiration and collapse of respiratory segments filled in water. Hyaline membranes appear as a result of coagulation of fragments of epithelial cells and proteins, penetrating the alveolar lumen through the damaged structures of aero-hematic barrier. All these changes occurring at the spontaneous or artificial breathing of premature animals with surfactant deficiency can be prevented by early preventive administration of surfactant prior to ventilation. It is stated that histological changes in lungs of premature animals are not observed practically after intratracheal instillation. So, surfactant not only improve aeration but reduces damages of bronchial and alveolar epithelium at early stages of development of RDS. Positive effect of exogenously administered surfactant were obtained in experiments on animals as a decreasing of diffusion of plasma proteins into the alveolar lumen [3, 9, 12, 13, 15].
Surfactant preparations have a broad application at the transfusion related acute lung injury (TRALI) and its most severe form – respiratory distress syndrome (ARDS) of adults and premature infants (PIRDS) – which is one of the most common reasons of mortality at critical states [13, 16, 17].

Abnormalities in surfactant system in patients with bronchiectatic disease are connected with stay period of causative agent in tracheobronchial tree and necessity to perform long-course therapy with antibiotics are given in the works of single researchers [2, 6, 12]. It was found that chronic inflammation is accompanied by the incidence of dystelectasis and atelectasis reason of which are morphofunctional changes in surfactant system as well as changes in ventilation and microcirculation [2, 3, 11]. That's why early recognition of surfactant-dependent changes of alveolar parenchyma has a great importance for their prophylaxis and correction [4].

Action of surfactant preparations and their substitutes is focused on the restoration of gas exchange function of lungs and prevention of development of respiratory distress caused by surfactant deficiency [16].

Another action of surfactant is activating influence on pulmonary macrophage for which it is a natural promoter of phagocytic activity through the receptor apparatus of macrophage [4, 7, 18]. All of the aforesaid makes development of complex therapy in patients with bronchiectatic disease is actual.

Prospective approach to the treatment of recurrences of BED is inhalation antibiotic therapy which is most physiological routes of administration of medicines in human body. Advantage of such therapy consists in preparation of medicinal products with high concentrations directly within the lesion, in increasing of active surface of medicinal product, in drug deposition in submucosa of bronchial wall. Besides, bypassing liver, medicinal products act more effectively at the respiratory tract and lung diseases. Negligible systemic toxic effect of medicinal product is observed. Local antibiotic therapy corresponds to the modern recommendations concerning inhibition of antibiotic resistance within population because systemic exposure is absent in result of purposeful drug delivery to the lesion and there is less risk of selection of resistant strains of normal flora [8].

This research provides use of inhalation method of administration of surfactant preparations at respiratory distress syndrome, pulmonary tuberculosis. We did not find applications of these specified techniques in patients with BED in available literature sources.

MATERIALS AND METHODS

This research is based on the studying of health outcome data of 61 patients with bronchiectatic disease in the exacerbation phase. These patients have undergone treatment in «V.T. Zaytsev Institute of General and Emergency Surgery of NAMS of Ukraine» over the 2009 to 2016 period. Main group consisted in 34 patients with BED, control group consisted in 27 patients.

Complex of clinical-laboratory examinations was performed on all patients with BED admitted to hospital. General state of patients was estimated by taking into account intended manipulations and volume of medication.

Plan radiography (in two projections) of thoracic organs was done obligatorily within a day of entry the hospital. Preliminary estimation of character pathologies, their localization and state of lung parenchyma was made based on the results of plan radiography.

Computed tomography (CT) of thoracic organs was put on to clarify patients' diagnosis.

Bronchoscopic examination was also performed. State of tracheobronchial tree was estimated. Sanitation and withdrawal of its content was done to perform bacteriologic and cytologic examination and to study parameters of sputum.

Intensive complex of traditional anti-inflammatory and pathogenic treatment was performed in arriving at a diagnosis and its cause factor.

Additional using of surfactant therapy according the proposed therapy was a difference in treatment of patients from main group.

Results of investigations in 17 healthy volunteers at the age of 18 – 25 years, for whom respiratory disorders were not observed, were used in this work for the purpose of comparison.

Concentration of general phospholipids in the condensate of expiratory air was determined for evaluation of state of the pulmonary surfactant system. Condensate of expiratory air was collected according to G.I. Sidorenko technique (1980, 1981). Patient was proposed to breathe out air into the condensate collection system. This device was like a spiral glass tube of a diameter up to 20 mm, immersed in a vessel with ice where was a temperature from 0 to -4 °C. Moisture settled on the walls of tube flowed down the bottom of receiving flask. This procedure was done in the morning after three-four-fold warm mouthwash.

Phospholipids of condensate of expiratory air were extracted according to Blur method. Extract was mineralized and inorganic phosphorous content was determined in residue (A.A. Pokrovskiy, 1969). Calculation of concentrations of general phospholipids (GPL, mmol/l) was done using calibration curve plotted with standard solution of potassium phosphate.

Cell count in bronchoalveolar liquid was performed. Resulting liquid was centrifugated, smears were prepared from the residue and stained with haematoxylin and eosin on Romanowsky procedure. Cell composition was determined. Ratio of alveolar macrophages, neutrophils, eosinophils and lymphocytes was expressed in per cents. Alveolar macrophages are of 87-93%, lymphocytes are of 7 – 10% and eosinophils are of less than 1% in cell composition of bronchoalveolar lavage. Neutrophils in endopulmonary cytogram of health person also don't occur (not more than 1.5%).

Functional test to measure rate of nasal mucociliary clearance was done acccording to the Kozlov B.I. procedure (2005). Physical properties of sputum were investigated: adhesiveness – based on degree of adhesion of sputum to glass (Plisko L.F., 1972), elasticity – based on yield strength, viscosity – based on flow time of liquid.

Statistical processing of the research results was carried out using personal computer PC-AT IBM 586 involving method of variation statistics, correlation analysis. Modifications of software package Statistica 5.0, Sts- grf, Biostat were applied.

RESULTS AND DISCUSSION

Surfactant preparations are known to be used in clinic for the treatment of infant respiratory distress syndrome, at acute lung injury in adults and also at pulmonary tuberculosis.

Based on the data about the state of surfactant system in patients with bronchiectatic disease, as well as the known properties of the surfactant preparations we started the study of their influence as a pathogenetic agent in conservative treatment of bronchiectatic disease.

At the present time in Ukraine preparation of exogenous surfactant Infasurf was registered, marketing authorisation number UA/9667/01/01 is valid from July 3, 2014 till July 3, 2019. Preparation is available in 3-mL or 6-mL vials. 1 mL of suspension contains 35 mg of phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg proteins including 0.26 mg of surfactant-associated proteins (SP-B and SP-C).

Intratracheal instillation is known for medicinal product Infasurf which is applied at respiratory distress syndrome (RDS) in premature infants. It is based on the introduction of the imulsion through the endotracheal tube at ventilation. However, taking into account the duration of exacerbations of bronchiectatic disease we considered use of these options as unacceptable.

Duration, fequency and cycling is necessary for pathogenetic therapy of patients with bronchiectatic disease, especially with drug resistance of microflora.

That's why we used method of administration of Infasurf which allows to perform abovementioned therapy by non-invasive procedure. It involves inhalation route of administration and selection of adequate single and total dose.
Known data about the mechanisms of physiological and therapeutic action of aerosol were background to investigation. Mucous membrane of airway and secretion, covering its surface, promote efficiency of retention of high desperasible aerosols. Ciliary activity ensures egestion of captured inhaled particles from respiratory tract. This

occurs normally. But the protective function that the ciliated epithelium provide for respiratory tract is lost at time consuming inflammatory process which is observed in patients with BED. Velocity of twinkling movement not only decelerates but mucoviscosity needed for adequate drain function is broken [2, 5, 6]. These changes are the greater the closer to lesion. Therefore, inhaled preparation of exogenous surfactant can absorb on the molecular receptors of airway cells. In other words, normalization of mucociliary clearance and increasing in phagocytic activity of pulmonary mononuclear cells are expected at adequate selection of particle size of artificially-administered surfactant.

Based on the theoretical justification mentioned above we worked out inhalation route of administration of exogenous surfactant preparations. Nebulizers enabling to generate particles with the size of 0.5 – 2 mm were used [8].

Selection of single and total course dose of preparation was quite difficult. Usage of high doses of surfactant replacement therapy in medical emergencies (distress syndrome), when dose of 105 mg of preparation (up to 4 doses) was instilled through a side port adapter into the proximal end of the endotracheal tube at longlasting course of disease, is unreasonable.

Phatogenetic therapy requires not only has “substitutive effect” and “normalize” quantitatively components of surfactant system but, first of all, activate and change qialitatively its functional properties. That's why we decided in favour of “small” oft-repeated doses of Infasurf. Determination of duration and doses of medicinal product was based on the studying of general phospholipids quantity in the condensate of expiratory air.

At the first stage we studied changing in concentration of general phospholipids in the condensate of expiratory air in patients with bronchiectatic disease depending on the beginning of exacerbation of disease in 20 patients and in 17 volunteers who didn't suffer from bronchopulmonary system diseases (table 1).

Table 1. Concentration of general phospholipids in the condensate of expiratory air depending on the beginning of BED exacerbation

	Time periods of exacerbation							
Concentration of general phospholipids mmol/l	Healthy volunteers	1 day	5 days	10 days	15 days	20 days	25 days	30 days
	0.017±0.002	0.012±0.001	0.009±0.002	0.007±0.002	0.007±0.002	0.008±0.002	0.009±0.001	0.010±0.002

Results, given in the table 1, shows that decreasing in concentrations of general phospholipids in the condensate of expiratory air in patients with BED is observed from the first days of exacerbation and it diminishes up to 20 days of exacerbation when slight increase is noted. The trend towards the increasing in general phospholipides concentration in the condensate of expiratory air in patients with bronchiectatic disease is observed up to 30 days of disease but it does not reach values recorded in healthy volunteers.

As can be seen from the above, it makes sense to perform inhalation surfactant therapy up to 20 days prior to the beginning of exacerbation.

Changing in general phospholipids concentration in the condensate of expiratory air in 40 patients with bronchiectatic disease was studied depending the dose and dose timing of medicinal product after inhalation in order to determine dosage and frequency of administration. Patients were underwent single nebulizer inhalation of preparation following which dynamics of general phospholipids concentration in the condensate of expiratory air was studied. Results are given in the table 2.

Studying of general phospholipids concentration in the condensate of expiratory air started in 6 hours after inhalation that is exposure time of dose at the treatment of respiratory distress syndrome. Further researches were carried out on 1, 2 and 3 days after inhalation.

Increasing in concentration of general phospholipids in the condensate of expiratory air was observed in all examinations in 6 hours after inhalation. Minimal increasing was noted at the inhalation of 0.75 mL of Infasurf.
Concentrations of general phospholipids in the condensate of expiratory air at the dose of 3 mL, 2 mL, 1 mL in 6 hours and within first days after inhalation didn't differ. Decreasing in concentration of general phospholipids was on the second day, that confirms data of pharmacological characteristics of preparation.

Downward trend of concentration of general phospholipids in the condensate of expiratory air is observed after inhalation of 0.75 mL of Infasurf that is explained by insufficient quantity of preparation at discussed disease.

Table 2. Concentration of general phospholipids in the condensate of expiratory air in patients with BED in the course of inhalation treatment

Dose	Original data	In 6 hours after inhalation	In 1 day	In 2 days	In 3 days	Healthy volunteers*
Infasurf 105 mg/3 mL (n=8)	0.010±0.001	0.014±0.001	0.014±0.002	0.012±0.001	0.011±0.001	0.017±0.002
Infasurf 70 mg/2 mL (n=8)	0.010±0.001	0.014±0.001	0.014±0.001	0.012±0.001	0.011±0.001	0.017±0.002
Infasurf 35 mg/1 mL (n=8)	0.010±0.001	0.014±0.001	0.014±0.001	0.012±0.001	0.010±0.001	0.017±0.002
Infasurf 26.25 mg/ 0.75 mL (n=8)	0.010±0.001	0.013±0.001	0.012±0.001	0.011±0.001	0.010±0.001	0.017±0.002

** - data about concentration of general phospholipids in condensate of expiratory air in healthy volunteers are given to compare dynamics*

One dose delivery did not increase concentration of general phocpholipids in condensate of expiratory air up to the parameters determined in healthy people in all observations. Specified changes prove necessity of long-term replacement therapy.

Minimal dose of Infasurf with therapeutic effect was 35 mg/1 mL, administered once daily. Taking into account that concentration of general phocpholipids in condensate of expiratory air didn't change for 1 day after inhalation, that's why we recommend to perform inhalation of Infasurf in patients with BED in the dose of 35 mg/1 mL once daily.
Therefore we recommend to perform inhalation treatment using nebulizer with Infasurf in the dose of 35 mg/1 mL once daily in patients with BED in one day during first 20 days from the start of acute exacerbation of disease.
Conservative therapy in patients of main group was added by the carrying out of inhalations with Infasurf in the dose of 35 mg/1 mL once daily using nebulizer in one day during first 20 days from the start of acute exacerbation of disease. Concentration of general phocpholipids in condensate of expiratory air in patients with bronchiectatic disease of both groups after conservative therapy is represented in table 3.

Table 3. Time course of general phocpholipids in condensate of expiratory air in patients with BED depending on the method of conservative treatment

Groups	Index
	Concentration of general phospholipids mmol/l
Healthy volunteers* (n=17)	0.017±0.002
Main group (n=34)	0.016±0.001
Control group (n=27)	0.012±0.002

** - data on healthy volunteers are given for comparison of dynamics*

In consideration of results, represented in table 3, we note that concentration of general phospholipids in condensate of expiratory air in patients of main group was near the indexes observed in healthy people. It was significantly lower than normal values in patients from comparison group, that points out the remaining gas exchange abnormalities.

A number of neutrophils in endopulmonary cytogram increases to 64-68%, while the number of alveolar macrophages reduces to 12 -15% at evident irritation which is observed in the system bronhus-lungs in patients with bronchiectatic disease.

Trend data of endopulmonary cytogram in patients with bronchiectatic disease is represented in table 4.

Table 4. Trend data of endopulmonary cytogram in patients with bronchiectatic disease under pressure of conservative therapy

Groups of patients	Alveolar macrophages		Neutrophils		Lymphocytes	
	prior to treatment	after treatment	prior to treatment	after treatment	prior to treatment	after treatment
Main group (n=34)	12 ±1.2	78±3.2	68 ±3.4	14±1.2	18 ± 2.6	14 ±1.1
Control group (n=27)	15 ± 1.3	42± 2.8	64 ±3.1	22 ±2.1	21± 1.8	17±.4

Reduced number of alveolar macrophages (AM) remains unchanged in the course of performed treatment in both groups. But in the study group content of alveolar macrophages increases by factor of 6.5 while in control group it increases by factor of 2.8. In addition, number of AM achieves nomal values in main group.

Decreasing of level of neutrophils in bronchoalveolar lavage occurs in the course of treatment too: in study group - by factor of 4.8 and in control group – by a factor of 2.9. This index is by 1.6 times better in patients from main group than in traditional treatment.

Lymphocyte level increases in both groups in the course of treatment but it does not achieve values of normal cytogram.

So, rising of index of neutrophils and decreasing in quantity of alveolar macrophages is typical for all patients with BED in the exacerbation phase. Level of neutrophils reduces in bronchial secretion but it does not achieve normal values. More evident positive dynamics was observed in patients of main group.

As cytologic examination in patients of control group shown, general quantity of macrophages of bronchoalveolar lavage remains reliably high (0.812± 0.024, inspite of 0.650 ± 0.012 x 10^6 normally) in the course of performed therapy. Although there is a downward trend in comparison with the beginning of an exacerbation of BED, the data is presented in table 5.

To the end of therapy viability of AM in patients of control group is 73.07 ± 0.936%, while in healthy volunteers of main gorup it is 91.88 ± 0.655. Relative percentage of these cellular elements in cytogram rises significantly but it is still reliably less than control values.

Table 5. Cytologic characteristic of alveolar macrophages of bronchoalveolar lavage in patients with BED in the course of conservative therapy

Groups of patients	A number of AM in 1 mL of bronchoalveolar lavage x 10^6	Viability of AM (%)	Relative amount of biosynthesizing AM (%)
Healthy volunteers* (n=17)	0.65±0.012	95.88±0.434	13.62±0.71
The beginning of an exacerbation (prior to treatment) (n=34)	0.898±0.039	42.82±0.230	41.52±0.91
Main group (n=34)	0.725±0.034	91.88±0.655	16.61±0.24
Control group (n=27)	0.812±0.024	73.07±0.936	29.72±0.83

** - data on healthy volunteers are given to compare dynamics, p <0.001*

Investigation of physical properties of sputum in patients of main and control group after course of conservative therapy is represented in table 6.

After the study of the measurement results of the physical properties of sputum, we note a more evident positive dynamics in patients of main group.

Table 6. Physical properties of sputum in patients with BED depending on method of conservative treatment

Groups	Viscosity mm^2/s	Elasticity $dine/cm^2$	Adhesion H/m^2
Healthy volunteers* (n=17)	9.3±1.6	16.3±2.3	0.5±0.1
Main group (n=34)	10.8±0.9	15.9±1.6	0.7±0.1
Control group (n=27)	15.7±1.4	14.8±1.6	0.8±0.1

** - data on healthy volunteers are given to compare dynamics*

Consequently, application of proposed procedures for treatment of patients in main group showed their evident positive influence on the dynamics of healing of chronic recurrent irritation. Application of proposed complex approach allowed to shorten area of irritation significantly, decrease or even eliminate its activity as evidenced by low level in bronchoalveolar lavage of “young” biosynthesizing macrophages, normalization of pattern of these cells subpopulations. Normalization of physical properties of sputum was observed.

CONCLUSION

After the study of nature of changes in concentration of phospholipids in the condensate of expiratory air in patients of main group; cytologic changes of sputum and characteristics of alveolar macrophages we came to conclusion that proposed procedure of conservative therapy of BED prevails over the traditional therapy. This makes it possible to recommend introduction of surfactant therapy in the complex treatment of BED.

REFERENCES

[1] A.I. Sinopalnikov, Ya.N. Shoihet. *Ukrainian pulmonology journal*, **2011**, 1, 75–82. [In Russian]
[2] M. Vendrem, R. Giron, De J Gracia. *Pulmonology*, **2010**, 5, 15–26. [In Russian]
[3] V.V. Erohin, O.V. Lovacheva, L.N. Lepeha, I.A. Vasileva, T.R. Bagdasaryan, O.A. Rosenberg. Complex treatment of destructive pulmonary tuberculosis using preparation of natural surfactant «surfactant-BL»: Guideline, **2010**; 22 pp. [In Russian]
[4] L.N. Lepeha, V.V. Erohin. *Problem of tuberculosis*, **2003**, 3, 51–24. [In Russian]
[5] A.Yu. Luschaev. *Valeology*, **2008**, 3, 71. [In Russian]
[6] Ya.N. Shoihet et al. *Siberian Medical Journal*, **2007**, 2, 25–29. [In Russian]
[7] K.S. Meyer, J. Regh, R. Baugman. *Pulmonology*, **2012**, 4, 17–27. [In Russian]
[8] M.N. Nephedova, E.I. Shmelev. *Tuberculosis and lung diseases*, **2008**, 8, 8–11. [In Russian]
[9] O. Ya. Svirskaya. *Health Care*, **2008**, 9, 57–60. [In Russian]
[10] O. Ya. Svirskaya, Yu. A. Ustinovich. *Med. Panorama*, **2012**, 2, 51–53. [In Russian]
[11] A.I. Sinopalnikov, A.A. Zaitsev. *Attending doctor*, **2009**, 10, 45–49. [In Russian]
[12] N.I. Starodumov, I.O. Prohorenko. *Morphological Newsletter*, **2011**, 2, 115–119. [In Russian]
[13] K. U. Vilchuk, O. Ya. Svirskaya, T. V. Gnedko Technology of administration of medicinal products containing surfactant to premature infants with respiratory distress syndrome: instructions for use No 075–0711, Minsk, **2012**; 8 p. [In Russian]
[14] Yu. A. Ustinovich, O. Ya. Svirskaya. *Health Care*, **2010**, 8, 60–63. [In Russian]
[15] U. Chotigeat, N. Promwong, W. Kanjanapattanakul et al. *J Med Assoc Thai*, **2008**, 91, 3, 109–114.
[16] H. Meng, Y. Sun, J. Lu et al. *J. Cardiothorac. Vasc. Anesth*, **2012**, 26, 5, 849–856.
[17] K. Raghavendran, D. Willson, R. H. Notter. *Crit. Care Clin*, **2011**, 27, 3, 525–559.
[18] D.G. Sweet, H.L. Halliday. *Arch Dis Child Educ Pract Ed*, **2009**, 94, 3, 78–83.