Eur Respir J, 1993, 6, 1427–1428
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European Respiratory Journal
ISSN 0903 - 1936

EDITORIAL

Is it rational to treat pneumonia with exogenous surfactant?

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Pneumonia is an important cause of respiratory failure, and is associated with increased alveolar permeability leading to pulmonary oedema, haemorrhage and atelectasis [1, 2]. The pathophysiological changes in pneumonia include hypoxaemia, decreased functional residual capacity (FRC), decreased total lung capacity (TLC), decreased lung compliance, and a diminished surfactant system [3–5].

As early as 1964, SUTNICK and SOLOFF [1] demonstrated that the surface tension of bronchoalveolar lavage (BAL) fluid from lung tissue with pneumonia was increased. They suggested that the pulmonary surfactant became inactivated and was responsible for atelectasis. Since then, it has been demonstrated that the surfactant system is impaired in bacterial [5], and viral pneumonia [6], as well as in *Pneumocystis carinii* pneumonia [7, 8]. These observations are based on the following findings.

In bacterial pneumonia, surface tension of BAL fluid is increased, whereas surfactant protein A (SP-A) content, total surfactant-lipids, the lecithin/sphingomyelin ratio, phosphatidylglycerol (PG), phosphatidylcholine (PC), and the amount of palmitic acid in PC, are all significantly decreased [5, 9]. Morphological changes in type II pneumocytes, which produce surfactant have been observed [2], and one could expect that surfactant of normal composition is no longer synthesized.

In viral pneumonia, STINSON *et al.* [6] demonstrated that pulmonary surfactant activity is decreased. These workers suggested that injury and destruction of type II pneumocytes by the virus were the cause of reduced surfactant activity, and may contribute to pulmonary collapse.

Recently, surfactant abnormalities have been demonstrated in human immunodeficiency virus (HIV) positive patients with *Pneumocystis carinii* pneumonia [7, 8]. In these patients qualitative and quantitative changes were seen in the surfactant composition, as well as increased phospholipase A_2 activity [8].

It is known that pulmonary surfactant is a carpet of lipids and specific proteins coating the interior of the lung, thus preventing end-expiratory collapse of the alveoli and small airways [10]. An intact surfactant system is also essential to maintain the fluid balance in the lung [11]. Destruction or inactivation of the surfactant results in alveolar collapse and pulmonary oedema [12]. It has also been demonstrated that surfactant plays a role in the lung's defence against infection [13]. In addition, surfactant, and in particular SP-A, enhance the antibacterial and antiviral defence of alveolar macrophages [13].

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Bacteria, bacterial toxins, viruses, phospholipases and proteinases released from inflammatory cells interact either directly with the surfactant film, or damage the endothelial and epithelial cells, leading to high permeability oedema [5, 14]. It is well-established that plasma proteins of the oedema fluid inactivate the surfactant [12]. Due to the decreased surfactant activity, surface tension at the alveolar walls increases, leading to increased suction forces across the alveolar-capillary membrane [11]. This finally results in a vicious circle.

Thus, there is evidence of a deficiency of active pulmonary surfactant in patients with pneumonia, which would be the rationale for exogenous surfactant therapy. We recently demonstrated the effectiveness of surfactant therapy in different animal models suffering from viral pneumonia or *Pneumocystis carinii* pneumonia [15–17]. In viral pneumonia, tracheal administration of exogenous surfactant led to improved lung compliance and improved FRC [15], as well as to restoration of gas exchange [16]. Also, in rats with *Pneumocystis carinii* pneumonia, surfactant instillation led to an improvement of blood gases [17]. The therapeutic dosage in all these experimental studies was 200 mg surfactant-phospholipids·kg^{-1} body weight. These results show that there was a shortage of functional alveolar surfactant in the animals with infected lungs.

A few preliminary reports indicate that instillation of exogenous surfactant might be efficacious in patients with adult respiratory distress syndrome (ARDS) [18]. We have treated a terminal patient with sepsis and severe ARDS [19]. Tracheal instillation of a natural surfactant (300 mg surfactant-phospholipids·kg^{-1} body weight) led, within 4 h, to a dramatic improvement in gas exchange (arterial oxygen tension (Pa_{O_2}) increased from 19 to 240 mmHg (2.5 to 32 kPa), arterial carbon dioxide tension (Pa_{CO_2}) decreased from 68 to 45 mmHg (9 to 6 kPa)). Chest X-rays, made 20 min before surfactant instillation and 4 h later, clearly showed that a nearly "normal" situation had been restored within this short period of time. These results show that the lungs of a patient with ARDS, superimposed with bacterial and viral pneumonia, can be re-aerated by tracheal instillation of exogenous surfactant.

In this issue of The Journal, MIKAWA *et al.* [20] are the first to report an improvement of oxygenation after selective instillation of exogenous surfactant in an adult patient with lobar bacterial pneumonia. A Gram-negative bacterium, *Morganella morganii,* was isolated in the sputum. The surfactant was instilled *via* a bronchofibrescope, which enables deposition of a small amount of surfactant in the infected lobe only. This method of instillation was probably chosen due to the prohibitive price of surfactant and the

non-availability of sufficiently large amounts of surfactant for use in adults. Immediately after surfactant application, oxygenation increased; this improvement was not dramatic but this may be attributed to the low dose of surfactant (240 mg) given. One may speculate that if surfactant had been administered to the whole right lung, the increase in oxygenation would be more striking.

The reported experimental and clinical findings support the role of exogenous surfactant therapy in bacterial, viral and *Pneumocytis carinii* pneumonia. Pneumonia and ARDS are closely associated. Not only is ARDS often complicated by nosocomial infections, but infection can also lead to ARDS [21].

Evidently, it is rational to administer exogenous surfactant in infected lungs, but the question then arises why is this not yet a reality. Surfactant has been commercially available for infants for about 5 yrs; if one were only to apply the dosage used for neonates (100 mg surfactant·kg^{-1} body weight) in adult patients, the amount of surfactant needed would be at least 7–10 g. At current prices, the costs of one treatment for one adult would then be 30,000–50,000 ECUs.

The rationale for giving surfactant is always to recruit collapsed alveoli and to stabilize them with the applied ventilator settings. Thus, before exogenous surfactant therapy is applied, one has to evaluate, by lung function tests, whether or not sufficient parts of recruitable lung areas are still available. Thus, one should not give surfactant to patients with heavily consolidated and/or fibrotic lungs, in which surfactant could not effectively improve lung function.

As soon as surfactant preparations become more widely available at lower costs, trials should begin to define the role of surfactant treatment in adults with pneumonia. For the future, one may also speculate on the use of surfactant as a carrier-substance for antimicrobial drugs, thus achieving high intra-alveolar drug concentration, and preventing high toxic systemic concentrations.

Acknowledgement: The authors thank L. Visser-Isles for assistance with English language editing.

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