Treatment of pulmonary surfactant deficiency. A clinical and experimental study.
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Document Version
Publisher’s PDF, also known as Version of record

Publication date:
1988

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
10.1 Introduction

The background of the present study is of clinical origin: the newborn baby with respiratory insufficiency due to surfactant deficiency (hyaline membrane disease). Until the beginning of this decade only supportive treatment was possible for these patients. The report on surfactant replacement therapy of Fujiwara et al. (1) initiated a new era in treatment of patients with hyaline membrane disease. Although the first results of this new approach of hyaline membrane disease are promising, it is also clear that the disease can not be treated successfully in all patients.

10.2 Clinical study

From 1985-1987 we participated in an international multicenter clinical trial on surfactant treatment in severe hyaline membrane disease. Apart from studying the long term effects of surfactant treatment we focused on the short term effects, as described in chapter 2. We found that surfactant treatment results in an increase in arterial PO2, followed by a decrease within 4 hours. Similarly the improvement of the chest radiograph following treatment was not sustained in all patients. These results and the outcome of other clinical studies directed us to further research with the overall goal to investigate factors that influence the results of surfactant treatment in surfactant deficiency.

10.3 Experimental study

Our aim was to determine the effects of different types of artificial ventilation on tissue of airways and lung parenchyma, and also perform biochemical and immuno-histochemical procedures in the lungs of surfactant deficient subjects. It is obvious that such studies can not be carried out in newborn babies for ethical reasons. We therefore studied aspects of surfactant deficiency in an animal model. Out of the various animal models of surfactant deficiency (chapter 4) we chose the lung lavage procedure to induce surfactant deficiency in 3-month-old rabbits. Lung function can easily be assessed by measurement of pH and blood gases from samples taken from an intra arterial catheter, in vivo static compliance of lungs and chestwall, in vitro pressure-volume characteristics of the excised lungs.

In chapter 5 the effects of high-frequency jet ventilation and conventional ventilation on lung function and tissue of airways and lung parenchyma in surfactant deficient rabbits are described. From the literature it is known that with high-frequency ventilation adequate gas exchange is achieved at lower mean airway pressure than applied during conventional artificial ventilation. Hence, a lower degree of barotrauma might occur during high-frequency ventilation. We found that high-frequency jet
ventilation results in a higher arterial PO2 and higher static compliance of the lungs than conventionally ventilated surfactant deficient rabbits. However, severe histopathological changes were found not only in the airways but also in the lung parenchyma of the high-frequency jet ventilated animals. We therefore conclude that although this mode of artificial ventilation has some attractive features, the possible side effects of high-frequency jet ventilation when applied in different lung diseases need further investigation.

Chapter 6 describes the effects of endotracheal administration of natural surfactant to surfactant deficient rabbits. Lung function was studied but as an ultimate test of the surfactant treatment the rabbits were subjected to a weaning off the artificial ventilation regimen. It was demonstrated that surfactant administration resulted in an instantaneous rise of the arterial PO2. The surfactant treated animals sustained the weaning procedure and re-established spontaneous breathing in room air, while maintaining normal blood gases. Furthermore, compared to the control animals, the lungs of the surfactant treated rabbits had better pressure-volume characteristics in vitro. To investigate whether the instilled surfactant participates in the metabolism of surfactant, the lamellar body fraction of the type II alveolar cells was isolated. We found that 28% of the instilled amount of surfactant phospholipids was present in this fraction. Based on these results we conclude that administered surfactant indeed is metabolized in the type II alveolar cell. Since the lamellar body is the intra cellular storage site of surfactant, we speculate that the administered surfactant is resecreted into the alveolar space and is reutilized. The clinical impact of this observation is not yet clear, but we assume that reutilization of administered surfactant is of importance for a sustained improvement of lung function in surfactant treated patients.

Chapter 7 describes a comparison between a natural sheep surfactant and an artificial porcine surfactant with respect to the surface properties in vitro and response of surfactant deficient rabbits. The aim of the study was to investigate whether the artificial porcine surfactant which is used in clinical trials is as effective as natural surfactant. The background of this study is that surfactant preparations have been introduced, that contain less protein than the natural surfactant. The protein is removed from the surfactant to avoid immunological reactions when used in patients. We found that the surface properties in vitro of the artificial porcine surfactant are better than those of natural sheep surfactant. However, both surfactant preparations improved lung function of surfactant deficient rabbits in such a way that spontaneous breathing in room air was re-established. The differences in lung function in favour of the group of animals that were treated with natural sheep surfactant could not be explained from the surface properties of the surfactants in vitro. Hence, for the treatment of newborn infants with hyaline membrane disease the tested artificial porcine surfactant has proved to be effective. The incomplete success of surfactant treatment i.e. the relapse of lung function after initial improvement, that was observed in the newborn infants, has to be explained by other mechanisms. The distribution and clearance of the instilled surfactant and effects on the respect.

To study the distribution method we prepared a monoclonal antibody in combination with the enzyme alkaline phosphatase. In frozen lung tissue sections of five full-term newborn infants with hyaline membrane disease it is demonstrated that the surfactant deficient subjects encounter the fact that the results of the disease performed so far are not encouraging. In principle the best surfactant for newborn infants with hyaline membrane disease performed so far are microsurgical sections of five full-term newborn infants with hyaline membrane disease the tested artificial porcine surfactant has proved to be effective. The incomplete success of surfactant treatment i.e. the relapse of lung function after initial improvement, that was observed in the newborn infants, has to be explained by other mechanisms. The distribution and clearance of the instilled surfactant and effects on the respect.

Research in this field must focus on the development of an artificial surfactant preparation that can be administered to newborn infants with hyaline membrane disease. The incomplete success of surfactant treatment i.e. the relapse of lung function after initial improvement, that was observed in the newborn infants, has to be explained by other mechanisms. The distribution and clearance of the instilled surfactant and effects on the respect.
surfactant and effects on the surfactant metabolism might be of importance in this respect. To study the distribution of artificial porcine surfactant by an immunohistochemical method we prepared a monoclonal antibody against a protein fraction of the surfactant. In frozen lung tissue specimens the porcine surfactant can be localized with this monoclonal antibody in combination with a peroxidase staining technique. In chapter 8 it is demonstrated that the surfactant is located in only 10% of the alveolar spaces of the lungs of surfactant deficient rabbits, at 4 1/2 hour after the endotracheal instillation. Since the treated surfactant deficient rabbits showed such an improvement in lung function that they re-established breathing in room air we speculate that the instilled surfactant is still present in the lung. Our hypothesis is that the surfactant has been taken up by the type II alveolar cells (chapter 6), presumably followed by resecretion. After the complex intracellular pathways the surfactant phospholipids are resecreted apparently separate from the apoprotein.

Chapter 9 describes the clearance of artificial porcine surfactant in premature surfactant deficient rabbits, using the immunohistochemical method of the previous chapter. It is demonstrated that most of the surfactant that was present in alveolar spaces and bronchi at 30 min after instillation disappeared in the next 90 min. Concomitant with the decrease of the surfactant in the alveolar spaces we found a decrease of the chest-wall-lung compliance. This might indicate that in the premature rabbit the disappearance of the instilled surfactant (transport via the lymphatic ducts and uptake by the type II alveolar cells) is not accompanied by sufficient resecretion of surfactant. It could be speculated that the rapid clearance of surfactant from the premature lung is the result of the inability of the type II alveolar cells to reutilize the administered surfactant.

10.4 Future developments

To date there is sufficient evidence that the endotracheal administration of surfactant in surfactant deficient subjects results in improvement of lung function. However we encounter the fact that the results of the clinical trials in patients with hyaline membrane disease performed so far are not quite satisfactory. Research in this field must be continued clinically to discover the optimal strategy for newborn infants with hyaline membrane disease. In this respect we believe that early treatment and multiple doses are of importance. Furthermore attention should be paid to the development of an artificial ventilator that can operate at high respiratory rates at low mean airway pressures, but does not cause lesions in the airways and lung parenchyma.

In principle the best surfactant to treat newborns is human surfactant. However, human surfactant is difficult to produce in large amounts. Amniotic fluid obtained by cesarean sections of five full term pregnancies is required to treat one patient with a single dose (2) It is to be expected that in the future synthetic human surfactant, a mix-
ture of phospholipids and synthetic apoproteins will be available. The coding sequence of the SP-A protein and the amino acid sequence of the SP-B have been characterized recently (3,4). Reconstitution of surfactant using human apoprotein SP-A, derived from amniotic fluid with a phospholipid mixture resulted in a biophysically active surfactant both in vitro as in vivo (5). Until synthetic human surfactant will be produced in large amounts, treatment with heterologous surfactant will be continued. So far no immunological responses following treatment with heterologous surfactant have been reported, but when multiple dose treatment will be applied on larger scale it is to be expected that an immune response is inevitable. The clinical impact of future immunological reactions after surfactant treatment is not yet clear. On the other hand in our opinion treatment with exogenous surfactant with the aim to reduce the incidence of the well known serious long term complications of hyaline membrane disease i.e. bronchopulmonary dysplasia and neuro developmental disorders is justified.

Apart from clinical studies, research focused on the metabolism of surfactant in the type II alveolar cell must be continued. Factors should be identified that influence the uptake of surfactant in the type II cells, factors that promote the secretion of surfactant and factors that influence the catabolism of surfactant. When we understand more of these processes we might be able to influence the surfactant metabolism in such a way that ultimately surfactant deficiency in premature newborn infants will be prevented.

References

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