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SURFACTANT AND RESPIRATORY DISTRESS SYNDROME*

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Since the late 1950s it has been known that the cause of respiratory distress syndrome (RDS) is surfactant deficiency, especially in preterm infants. But surfactant protein B deficiency may cause RDS in term infants as well. Administration of natural surfactant produce is well known to a rapid improvement in oxygenation within 15 to 20 minutes. The effect of synthetic surfactant is less dramatic. Although randomized controlled trials have been done, the majority have been relatively small. Studies on the role of natural surfactant given to infants with established RDS (rescue therapy) have shown a reduction in the incidence of neonatal death and pneumothorax of 40% and 65%, respectively, compared to untreated infants. However, natural surfactant provides no apparent benefits in terms of the incidence of intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA) or bronchopulmonary dysplasia (BPD). The results of synthetic surfactant given as rescue therapy have shown a similar effect with a 40% reduction in mortality and a 48% reduction in pneumothorax. However, synthetic surfactant also led to a 23% reduction in IVH, 27% in PDA, and 32% in BPD. When natural surfactant is given as prophylaxis (i.e. at or soon after birth, before the development of RDS), the reduction in mortality is 45% and the reduction in pneumothorax is 69%, but as with rescue therapy, there is no effect on the incidence of IVH or BPD. The effect on the incidence of PDA is an increase of 27%. When synthetic surfactants are given prophylactically, there is a similar reduction in mortality of 44% and a reduction in pneumothorax of 36%. The incidence of IVH and BPD is unchanged, but as with the natural surfactant, there is a small increase in the incidence of PDA of 27%. The main side effect is pulmonary hemorrhage that has been reported to occur in 4-7% of infants given surfactant. Although the administration of surfactant has had a dramatic effect on neonatal practice, it is likely that further studies will lead to more appropriate use of surfactant. *Key words: surfactant, respiratory distress syndrome, mortality, morbidity, side effects.*

Function of Surfactant

Although there has been great interest in the role of surfactant in the lung, it is also found in all cavities, including the joints, pleural and pericardial spaces. It then functions as a highly efficient lubricant with qualities far exceeding commercial engine oils!

It has been known since the late 1950s[1] that lack of surfactant in respiratory distress syndrome reduces lung compliance by increasing surface tension forces at the air/water interface within the alveoli. However, when a surfactant preparation is tested in the laboratory using the Wilhelmy balance, the effects initially seem disappointing as the surface tension of pure water is only reduced from 70 to

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approximately 40 dynes/cm. Adding plasma has a similar effect, while a detergent such as Tween 80 will reduce the surface tension force down to 30 dynes[2]. If, however, the surface area is then reduced by moving a strip in contact with the surface towards one end, the surface tension measurement will drop effectively to zero after the addition of surfactant, but remain at 30 when Tween 80 has been added[2]. This is an illustration of the third important role of surfactant, that of providing alveolar stability. This dynamic effect of surfactant results from the concentration of the monolayer of molecules each with a hydrophylic end in the water and hydrophobic end in the air space above. Thus, on expiration there is a continuous film of lipid lining the alveoli, rather like a waxy coating, and the water molecules are no longer in contact with the air. This also has the effect of solidifying the surface. This can be demonstrated by adding a very light object to the surfactant/water film in the Wilhelmy trough. While the surface area is relatively large, the object can readily be blown from side to side. When, however, the surface area is reduced so that the surfactant molecules are packed together, the object remains stationary despite vigorous blowing, indicating that the surface is no longer liquid[3].

The fourth function of surfactant is that of lung clearance. On each inspiration, surfactant molecules are recruited to the surface as the alveolar area increases. On expiration, there is then an excess of surfactant molecules which pass from the alveoli to the small airways.

In this way, micro-particles such as bacteria are carried on the surface film from the alveoli to the 14th and 15th division of the airways, where cilial action takes over the function of surfactant as the main lung clearance mechanism[4].

Role of Surfactant Proteins

Although the main constituents of surfactant are phospholipids, the major one being dipalmityl phosphatidyl choline, five to 10 percent consists of surfactant proteins. There has been increasing interest in recent years in the function of these different proteins. Surfactant A appears to have an important role in regulating the rate of surfactant secretion and recycling, and also improves surfactant structure[5]. Surfactant B enhances the formation of the surfactant monolayer and improves spreading[6,7]. It also has a direct effect in reducing surface tension. Surfactant C protein also enhances film formation, while surfactant D appears to have a role in surfactant metabolism and may be important in immune defenses of the lung[8,9]. Surfactant B and C are produced in relatively small quantities before 20 weeks' gestation, but then, unlike surfactant A, rise rapidly[10]. Surfactant B deficiency appears to be responsible for the occurrence of respiratory distress syndrome (RDS) in relatively mature babies born to diabetic mothers, and is also responsible for the occurrence of respiratory distress syndrome in term babies born to susceptible families[11].

The Physiological Effects of Surfactant Administration to Babies with RDS

As could be anticipated from physiological studies on surfactant function in the laboratory, respiratory distress syndrome is associated with stiff, small and relatively airless lungs. It is well documented that the administration of natural surfactant produces a rapid improvement in oxygenation so that the $aaDO_2$ may fall from 300-400 mmHg to 30-40 within 15 to 20 minutes. The effects of synthetic surfactant, such as Exosurf, are less dramatic. With this it is often difficult to determine whether the surfactant is having a therapeutic effect in less than six hours. It was anticipated that these improvements in oxygenation would be associated with corresponding improvements in the compliance measurements, indicating that the lungs were no longer so stiff. However, the majority of studies failed to show any improvement in compliance measurements obtained by relating the volume of gas entering and leaving the lung to the ventilator pressure swing, at any rate, until 12 or even 24 hours after the improvement in oxygenation[12, 13].

Other investigators have shown that improvement can be noted early provided that true, static compliance measurements are obtained[14]. These are achieved by occluding the airway at the end of inspiration, which will eliminate all respiratory effort via the Hering Breuer inflationary reflex, and then venting the gas from the lung to ambient rather than to positive end expiratory pressure (PEEP). An elegant study by Kelly et al.[15] confirmed very clearly that improvement in lung compliance can only be demonstrated early after the adminstration of surfactant, if this method of measuring compliance is used, rather than purely by relating the tidal volume to the ventilator pressures.

There have now been a small number of studies measuring the lung volume of babies requiring ventilatory therapy for respiratory distress syndrome, both before and after administration of surfactant. These have usually depended on measuring the concentration of an insoluble tracer gas such as helium or argon in a small rubber bag within a cylinder, arranging for the ventilator to provide respiratory support to the baby via the bag rather than directly via the endotracheal tube for 30 to 45 seconds. These have shown that lung volume in severe respiratory distress syndrome may be as low as 5 ml/kg of body weight[16], compared to a normal of 25. Studies including our own[16, 17, 18] have shown that after natural surfactant, there is a rapid rise in lung volume, although not to normal levels[16, 18]. The effects of synthetic surfactants are less dramatic.

It is also possible to use this technique to measure the effective pulmonary blood flow, i.e., the blood supply to alveoli which are being adequately ventilated. This is achieved by adding a second test gas which is highly soluble in water, such as freon 22 or acetylene[19]. During the re-breathing period, the concentration of this gas will continue to decay, whereas the insoluble gas will stabilize after about

20 to 30 seconds. By knowing the solubility of the gas in plasma and the concentration of the soluble gas within the alveoli at each breath, it is possible to measure the effective pulmonary blood flow with good reproducibilty. These studies have shown that after natural surfactant, there is a significant increase in the effective pulmonary blood flow, although these improvements are smaller than the changes in the lung volumes[18].

It remains surprising to many people that surfactant therapy leads to improvement in lung volume and yet has no obvious effect on lung compliance as determined by the volume delivered by the ventilator. There have, however, been two studies which have helped to resolve this problem. The first one indicated that the major effects of surfactant therapy on the deflation curve of surfactant-deficient piglet lungs was at pressures of less than 5 cm H_2O, i.e., the pressure volume slope above this pressure was little changed by the addition of surfactant[19]. This indicated that surfactant was having its maximum effect at low inflation pressures, i.e., at or below the PEEP levels currently used. A further study examined the effects of PEEP on lung volumes before and after the administration of surfactant, also showing that the main effect of surfactant was at low lung volumes and pressure[20]. This raises the exciting possibility that as oxygenation improves after the administration of surfactant, small reductions in PEEP may so greatly increase the tidal exchange that the peak pressure can be reduced considerably.

Side Effects of Surfactant Therapy

There are now a number of studies showing that the rapid administration of large volumes of surfactant, for example, giving 5 mls/kg of body weight of Exosurf over two to three minutes, can produce increases in cerebral blood flow as measured by Doppler techniques[21]. These increases are in the order of 30 to 40 percent and are partially, although not totally, explained by a temporary increase in CO_2 retention due to poor ventilation. It would therefore seem sensible to give large volumes of fluid to the airway at a relatively slow rate. The second complication is that of pulmonary hemorrhage, which has been reported to occur in four to seven percent of babies given surfactant[2]. Hemorrhage is usually, though not always, relatively mild, but most authorities consider the presence of pulmonary hemorrhage to be contraindication to surfactant therapy. A third anxiety has been that giving natural surfactant, which inevitably contains animal protein, might induce immune responses in the months after its administration[23].

Finally, there has been some anxiety that the administration of surfactant might impair responses to infection within the lungs. It has been noted that the macrophages in particular tend to take up the surfactant, and concern has been

expressed that this might interfere with their function. There is however no clinical evidence that babies given surfactant have an increased incidence of lower respiratory tract infections, and indeed, increasing evidence that pre-term babies with congenital pneumonia are likely to be helped by surfactant administration.

Clinical Studies on the Role of Surfactant Therapy

There are now two synthetic and at least five natural surfactants available for the treatment of respiratory distress syndrome in pre-term babies. Although randomized controlled trials have been carried out, the majority of these have been relatively small. In order to make the best use of all the information available, a number of meta analyses have been carried out combining the information from a number of studies with similar designs. These have provided current knowledge as to the best way to give surfactant therapy. Studies on the role of natural surfactant given to infants who have established respiratory distress syndrome, i.e., rescue therapy, have shown that when compared to untreated infants there is a reduction in neonatal death of approximately 40 percent, with 95 percent confidence limits ranging from 16 to 57 percent. The incidence of pneumothorax is reduced by approximately 65 percent with confidence limits of 56-73 percent. There are, however, no apparent benefits regarding the incidence of intraventricular hemorrhage, patent ductus arteriosus or subsequent bronchopulmonary dysplasia. The results of synthetic surfactant given as rescue therapy (Exosurf) showed a similar effect with a reduction of approximately 40 percent in mortality and 48 percent (also below) in pneumothorax. Interestingly, Exosurf also led to a 23 percent reduction in IVH (confidence limits 3-38%) and a reduction in the incidence of patent ductus arteriosus of 27 percent (confidence limits 12-40%).

Of equal interest was the finding that Exosurf reduced the incidence of bronchopulmonary dysplasia by 32 percent (confidence intervals 1-54%). When natural surfactant is given as prophylaxis, i.e., at or soon after birth and before the development of respiratory distress syndrome, the reduction inmortality is slightly greater at 45 percent, with a confidence limit of 20 to 62 percent[24]. The pneumothorax rate showed a dramatic reduction by 69 percent, but as with rescue, there was no effect on the incidence of intraventricular hemorrhage or bronchopulmonary dysplasia. The effect on the incidence of patent ductus arteriosus was the opposite of that seen after rescue with synthetic surfactant, i.e., a small increase of 27 percent (confidence limits 3-57%). When synthetic surfactants including ALEC were given prophylactically, there was a similar reduction in mortality of 44 percent (confidence limits 26-57%) and a reduction in pneumothorax of 36 percent. The incidence of IVH and bronchopulmonary dysplasia was unchanged; however, as with the natural surfactant, there was a small increase in the incidence of patent ductus arteriosus of 27 percent, but no effect on the incidence of bronchopulmonary dysplasia[24].

The question of how many doses of surfactant should be given is obviously of considerable interest to clinicians. Current data indicates that with natural surfactant, two doses are preferable to one[25], but that with Exosurf, a synthetic surfactant, four doses have no advantage over two[26]. The number of infants included in studies comparing prophylaxis with rescue treatment has been relatively small. A meta analysis on these carried out by Soll suggested that prophylactic therapy[27] was probably associated with a reduction in the incidence of pneumothorax, but there was insufficient evidence to show a benefit in terms of mortality, IVH or bronchopulmonary dysplasia for either form of therapy.

Our information on the relative efficacy of synthetic and natural surfactants is also limited, but the latest meta analysis indicates that a natural surfactant (Survanta) will reduce mortality by approximately 10 percent more than will a synthetic surfactant (Exosurf). The author calculated that the use of a natural surfactant will save the life of an additional baby for every 33 treated.

Although the administration of surfactant has had a dramatic effect on neonatal practice, it is likely that further studies will lead to more appropriate use of surfactant. In the near future it is likely that synthetic surfactants will be available to which genetically engineered human surfactant proteins will have been added. Hopefully, these preparations will eventually become relatively inexpensive, and certainly would have the advantage that they would be totally free from foreign proteins.

Conclusion

We now have considerable information on the biochemistry and the physiological effects of surfactants. Although further fine tuning is likely to take place, we do now have sufficient information on how to use the currently available surfactant preparations effectively. There remains the problem of cost. It is hoped that in the next few years, market forces will improve so that infants throughout the world can have access to this life-saving form of therapy.

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