New targets for surfactant replacement therapy: experimental and clinical aspects

The benefits of surfactant replacement therapy for neonatal respiratory distress syndrome (RDS) have been well documented in several randomised trials, and this treatment is now part of routine clinical management of babies with immature lungs. Meta-analysis of data from a large number of babies treated in controlled trials has confirmed lower mortality and reduced incidence of complications, especially pneumothorax. This is also the case when surfactant is administered prophylactically to babies at risk soon after birth. These beneficial effects have been obtained with modified, natural, as well as with protein free synthetic surfactants.

The pathophysiology of neonatal RDS is characterised by a combination of surfactant deficiency and surfactant inactivation as a result of plasma proteins leaking into the air spaces from areas of epithelial disruption. Surfactant may be inactivated or deficient in other forms of lung disease as well, including meconium aspiration syndrome (MAS), pneumonia, lung hypoplasia, the "adult" type of acute respiratory distress syndrome (ARDS), and pulmonary haemorrhage. In this article I intend to outline experimental and clinical evidence indicating that these various diseases constitute potential new targets for surfactant replacement therapy.

Meconium aspiration syndrome

Aspiration of meconium elicits a complex series of pathophysiological events characterised by mechanical obstruction of airways, "chemical pneumonitis," and inactivation of surfactant. Meconium contains several components which interfere with surfactant function, including cholesterol, free fatty acids, and bilirubin. The inhibitory effect of meconium is dose dependent, but not simply due to the stoichiometric relation between inhibitor and surfactant. Low concentrations of surfactant are therefore relatively more sensitive to inhibition than high concentrations. For example, when examined with a pulsating bubble, modified natural surfactant at a concentration of 1.5 mg/ml is completely inactivated by a meconium concentration of 65 mg/ml. At a twofold higher surfactant concentration (3 mg/ml), as much as 1300 mg/ml of meconium is required to obtain the same inhibitory effect. Thus increasing the pool size of surfactant in the air spaces of a baby with MAS may not only counterbalance the presence of inhibitors but also makes the surfactant system relatively more resistant to inhibition. This is the rationale for surfactant therapy in MAS.

Promising effects of surfactant administration have been documented in animal models of MAS. Treatment with the clinically recommended dose of Curosurf improves lung compliance, gas exchange, and alveolar expansion in newborn rabbits and adult rats with experimental meconium aspiration but does not restore normal lung function. Improved oxygenation has also been observed in non-controlled studies on babies with MAS treated at a comparatively late stage of the disease with calf lung surfactant extract (CLSE) or bovine lung surfactant extract (BLES); however, the effect was less prominent than in term babies with RDS. In one of these studies it was pointed out that several of the babies with MAS, treated with surfactant, who were candidates for extracorporeal membrane oxygenation (ECMO) according to conventional criteria, survived without that intervention. Data from a recent randomised trial, evaluating the effect of Survanta in babies with MAS, indicate that better results are obtained if the treatment is given early and multiple doses are provided. MAS, therefore, clearly remains a potential new target for surfactant replacement therapy.

Pneumonia

Neonatal pneumonia caused by group B streptococci may masquerade as RDS, in part because endogenous surfactant could become inactivated by the inflammatory exudate. Several babies with neonatal group B streptococcus pneumonia have, in fact, received exogenous surfactant on the erroneous assumption that they suffered from primary surfactant deficiency. In this context, data from animal experiments are reassuring because they show that proliferation of group B streptococci in neonatal lung tissue is not stimulated by surfactant therapy. On the contrary, a reduction in bacterial growth has been reported in near-term rabbits infected with group B streptococci and treated with a synthetic surfactant substitute (Exosurf) or modified natural surfactant (Curosurf). Improved lung function has been observed in neonatal streptococcal pneumonia after treatment with Curosurf, suggesting a role for surfactant therapy. Perhaps surfactant fortified with SP-A and/or SP-D—two surfactant proteins stimulating alveolar macrophages—would be more effective and bacteriostatic than currently used modified natural surfactants containing only lipids and hydrophobic proteins.

Lung hypoplasia

The lungs of neonates with congenital diaphragmatic hernia (CDH) are not only small but also biochemically immature. Studies on experimental CDH induced in lambs by fetal surgery indicate that the stability of the hypoplastic lung(s) might be improved by treatment with exogenous surfactant. Clinical experience of surfactant therapy in CDH is limited to a few anecdotal cases showing a variable response, less impressive than that documented in babies with RDS, MAS, or congenital pneumonia. However, even a modest improvement in lung function may be important in critically ill babies with CDH, by reducing the need for aggressive ventilator treatment or ECMO.

ARDS

This is characterised by non-cardiogenic pulmonary oedema and secondary inactivation of surfactant by leaking plasma proteins. It may occur in any age group,
probably also in newborn babies.\textsuperscript{18} ARDS has a multifactorial pathogenesis and can be triggered by, for example, sepsisemia and severe asphyxia. An important element in the pathogenesis of ARDS is the entrapment of activated leucocytes in alveolar capillaries, with release of cytokines, reactive oxygen species, proteases and a variety of other mediators of tissue injury and increased microvascular permeability. Elastase released by inflammatory cells may also degrade surfactant associated proteins, further aggravating the situation.\textsuperscript{19} As in a baby with MAS or streptococcal pneumonia, the presence of surfactant inhibitors in the air spaces can at least in part be neutralised by upgrading the pool of intrapulmonary surfactant—that is, by replacement therapy. In patients with severe lung injury this may require large doses of surfactant. Treatment with surfactant may have a favourable influence on the course of ARDS by down-regulating the release of cytokines from inflammatory cells.\textsuperscript{17,19}

Promising results have been reported from clinical trials of surfactant therapy in adult patients with ARDS, both in a pilot study using Curosurf\textsuperscript{20} and in a large controlled study using Survanta.\textsuperscript{21} In the latter study airway instillation of surfactant at a total dose of 400 mg/kg (divided in 4 doses given at 6 hourly intervals) led to a significant reduction of both oxygen requirement and mortality. In contrast, a large clinical trial evaluating the efficacy of aerosolised synthetic surfactant (Exosurf) showed no improvement in physiological measurements compared with placebo treated patients, and mortality was identical in the two groups.\textsuperscript{22} This discrepancy in outcome between the two trials may reflect a difference in quality between the two surfactants tested, or ineffective deposition of the aerosolised material in the lungs, or a combination of both factors. Only anecdotal paediatric cases treated with surfactant have been reported\textsuperscript{23,24} and some of these seem to have responded satisfactorily. High resistance to activation by plasma proteins would probably be an important property of an exogenous surfactant designed for treatment of ARDS.

Other targets

Pulmonary haemorrhage, usually regarded as a possible complication of surfactant therapy, especially in very low birthweight babies, may respond favourably to exogenous surfactant,\textsuperscript{25} indicating an element of surfactant dysfunction in the pathophysiology of the disease. Improved oxygenation has also been observed in babies with early chronic lung disease treated with a single dose of BLES.\textsuperscript{26} Finally, it has been reported that babies receiving ECMO can be weaned more rapidly after multiple doses of Survanta.\textsuperscript{27} In contrast, babies with neonatal respiratory failure caused by congenital deficiency of surfactant protein B, respond only transiently to replacement therapy.\textsuperscript{28}

The increasing use of inhaled nitric oxide (NO) in patients with neonatal lung disease associated with high pulmonary vascular resistance raises a number of questions about potential interactions between this highly reactive molecule and surfactant. Synergistic effects between NO and exogenous surfactant need to be explored in animal models, and the possible toxic effects of NO on surfactant components should be carefully investigated before inhalation of NO becomes part of routine neonatal intensive care. Of particular concern is the recent observation that the structural and functional properties of SP-A may be damaged by exposure to peroxynitrite formed by a reaction between NO and superoxide released by activated inflammatory cells.\textsuperscript{29}

Conclusion

Indications for surfactant treatment in neonatal lung disease will probably become wider in coming years. In principle, any neonatal lung disease with an element for surfactant dysfunction constitutes a potential target for replacement therapy. Perhaps the next generation of exogenous surfactants will be more “customised” to match the clinical situation. For example, specific surfactant proteins could be added to increase resistance to inhibition and enhance bacteriostatic properties of preparations administered to patients with infection. Yet another potential, adding a new dimension to surfactant therapy, is the possible use of surfactant liposomes to improve intrapulmonary dispersion of antibiotics or other therapeutic agents administered via the airways.\textsuperscript{30}

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