How synthetic surfactants allowed those with RDS to breathe more easily

In The Journal's latest article on landmark drugs, Jenny Bryan looks at the role of synthetic surfactants in the competitive market for treatments of respiratory distress syndrome in premature babies

When the first synthetic form of surfactant (Exosurf) was launched in the UK in 1991, scientists thought they had finally overcome all the problems of mimicking the lung's natural lubricant, over 30 years after its role was identified. British pharmaceutical company Wellcome (now part of GlaxoSmithKline) had licensed Exosurf from its University of California inventor John Clements and leapfrogged to the front of what was becoming a competitive market for treatments of respiratory distress syndrome (RDS) in premature babies.

Sandra Calvert, consultant neonatologist at St George's Hospital, London, took part in one of the early trials of calf lung surfactant in Canada in the mid-1980s and recalls the challenges that researchers faced in getting a product with the right mix of lipids and proteins to lower alveolar surface tension and enable babies with RDS to breathe more easily.

“We knew that surfactant was produced from the 24th week of gestation onwards and that, without it, a baby's lungs would collapse after each expiration — making it harder and harder to breathe. Physiologically, it made sense to give surfactant but it took some time to understand what parts of the substance really mattered,” explains Dr Calvert.

An essential lubricant

Early experiments suggesting that surface tension might play an important role in determining the ability of babies to take their first breath were carried out by German physiologist Kurt von Neergaard in 1929.1 Further work on the effects of nerve gases in the lungs in the 1950s predicted that a natural substance in the alveoli was capable of reducing surface tension at the air-liquid interface.2 But it was Boston-based paediatricians who made the connection between increased alveolar surface tension and development of hyaline membrane disease (HMD) in premature babies and attributed it to a lack of surface active material, subsequently called surfactant.3 HMD is named after the glassy membrane of proteins and dead cells that form in the lining of the alveoli, making them stiff and unable to perform normal gas exchange.

“Before surfactant became available, babies with hyaline membrane disease needed high pressures of mechanical ventilation to help them breathe and this made their alveoli even stiffer, so it was a vicious circle. Once we had surfactant, we could use lower pressures, resulting in less damage and long-term scarring to babies' lungs. So it quickly became unethical not to use surfactant,” says Dr Calvert.

Natural or synthetic?

In the absence of human surfactant, the first studies in premature babies used natural or modified bovine surfactant, with promising...
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Pumactant, and with the natural bovine surfactant (Survanta) and porcine Curosurf, important differences in efficacy started to emerge. A Cochrane analysis published 10 years after Exosurf’s launch concluded that both natural and synthetic surfactant were effective in the treatment and prevention of RDS. But natural surfactant was associated with greater early improvement in requirement for ventilator support, fewer pneumothoraces and fewer deaths.

Around this time, Pumactant was withdrawn from the market after it was shown to have a statistically significantly higher pre-discharge mortality than poractan alfa. Demand for Exosurf gradually declined and the product is no longer marketed in the UK.

Research has continued into novel synthetic surfactants with added SP-B or SP-C, and a Cochrane review analysed data from two studies that compared lucinactan — a synthetic surfactant that contains peptide fragments mimicking parts of SP-B — with porcine or bovine surfactin. The meta-analysis suggested similar efficacy between lucinactan and the natural surfactants for prevention of RDS, incidence of chronic lung disease and other common complications of prematurity. There was a trend towards decreased mortality and a significant decrease in rates of necrotising enterocolitis with lucinactan. But the reviewers concluded that there was insufficient evidence to justify choosing between protein-containing synthetic surfactants and animal-derived surfactants for prevention of RDS, and added that there were no studies of protein containing synthetic surfactants to treat existing disease. US biotechnology company Discovery Laboratories is currently seeking marketing authorisation for lucinactan (Surfasin) for RDS prevention in the US.

Changing trends in practice

Surfactant was initially introduced to rescue babies with RDS, but neonologists soon started using it earlier in the management of premature infants. Current British guidelines recommend that all babies under 30 weeks’ gestation needing intubation should have surfactant as soon as possible after birth.

“It makes sense to give surfactant as prophylaxis rather than wait for the damage to be done, even in babies born before 24 weeks who wouldn’t yet be producing surfactant if they were still in the womb,” explains Dr Calvert. She points out that there is a move towards using nasal continuous positive airway pressure (CPAP) instead of mechanical ventilation in premature babies. But, even when this approach is used, babies are sometimes intubated in order to administer surfactant and then the tube withdrawn before switching to CPAP.

Dr Calvert concludes that it is a baby’s overall care rather than the decision to give CPAP or mechanical ventilation that is most important for reducing the risk of chronic lung disease, and surfactant is likely to play a major role for the foreseeable future.

“Surfactant reduces the amount of time that babies need to spend on ventilation and the less pressure on their airways, the less damage is done. The combination of surfactant and ventilation, and prenatal steroids for babies we know are going to be born prematurely, has had a huge impact over the past 30 years — helping to bring down the limit of viability from 26 weeks in the 1980s to 23 weeks today. Whatever changes are made to its lipids and proteins in the future, surfactant is certainly here to stay,” she says.

References
9 Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2001;(2):CD000114.