

## CONTROVERSY

## Surfactant replacement therapy—time for thought

G McClure

The era of surfactant replacement therapy is upon us—there are many such treatments and some are now becoming commercially available and we may expect claim and counterclaim among the clinical and commercial interests. Undoubtedly, such substances confer benefits to most of the recipients. The oxygenation of blood improves and in some studies a reduction in mortality has been reported.<sup>1</sup> As such, these achievements should be saluted; anything that clearly can be shown to benefit sick preterm infants should be widely employed.

Before this happens, however, clinicians should pause for mature reflection and study the published data in minute detail. What causes concern to some is that there may be misuse of these substances, that expectations may be too high, and that ultimately we may disillusion ourselves and conceivably may harm some of our patients.

Most trials have been multicentre as none of us have sufficient patients to provide answers in a working lifetime. Entry of patients into trials is therefore based on the clinical judgment of many separate individuals. This means that the possibility of inconsistency increases: if 20 neonatologists look at 100 breathless babies, it is unlikely that they will agree on a diagnosis in all cases. Further, it is unlikely that every baby enrolled in these trials was seen first by a consultant neonatologist as many will have been born in the middle of the night so the error may be further magnified by inexperience. In addition, management subsequent to surfactant administration varies within and between trials so it is difficult to discern clearly the whole truth.

However, this is not my major worry. It is possible that among the hundreds of babies who have received surfactant replacement therapy, there are some babies who might have been better left alone. I am really referring to the tiny, cold, asphyxiated baby who needs our help most but who is at the limit or is possibly beyond the range of our knowledge. It is possible that such babies will do badly no matter what is done after birth—they do not suffer only, or in some cases, at all from surfactant deficiency respiratory distress syndrome. In the opinion of some, these babies should be excluded from the trials but in many instances this is not the case. For example in the OSIRIS protocol of February 1990 the entry criteria do not exclude infants of extremely low birth weight or in poor condition at birth but it does state that there

should be 'no contraindications judged by the clinician responsible for care'. The Curosurf trials also made no exclusion for condition at birth.<sup>2</sup> The Exosurf trial, coordinated by Long,<sup>3</sup> excluded babies of  $\leq 750$  g but made no allowance for features such as low Apgar scores or hypothermia. These exclusions were similar to those in the SURVANTA trials.<sup>4</sup> While one accepts the extreme difficulty experienced by designers of major trials it might have been better had rigid entry criteria been employed and those extremely small babies already referred to were excluded.

There are two outstanding worries about the long term effects of respiratory therapy in these babies: bronchopulmonary dysplasia (BPD) and intraventricular haemorrhage (IVH). Morley in his recent review states that 'surfactant treatment has a variable effect on the incidence of BPD'.<sup>5</sup> Long, in explaining why BPD was not reduced in a trial of a synthetic surfactant (Exosurf) reasons that this problem may be dose related or may be due to a type II error because of the relatively small sample size in that study. This may be but we must not overlook perhaps more obvious explanations. This condition is caused by barotrauma and it is likely that the longer the duration of time that a baby stays on a ventilator, the more likely he or she is to develop BPD. Tiny babies may require ventilator assistance for reasons other than respiratory distress syndrome, they are extremely small and weak and may be unable to sustain respiration. It is therefore likely that these very small babies may require prolonged ventilation and therefore be at major risk of developing BPD.

Again the effect of surfactant therapy on the incidence of IVH is inconsistent.<sup>4-6</sup> This is scarcely surprising for a variety of reasons notably the fact that respiratory distress syndrome is not the only cause of IVH. This condition may occur in utero and, in many cases, may be preset to occur at a later stage by the time of delivery. Such babies are likely to be the smallest.

The effect of surfactant on mortality again varies, although there would appear to be an overall reduction. Merritt *et al*, quoting Hack and Fanaroff, state that there has been no overall reduction in deaths in babies of less than 750 g at birth in approximately the past decade.<sup>7</sup> These babies then present a major challenge but in the study of Merritt *et al* using human surfactant, although the mortality rate overall was significantly reduced 'the 17.5% of infants with birth weights of less

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than 0.75 kg accounted for 67% of all deaths'. They also state that 'the use of surfactant in infants of lower weights may improve survival rates but also may be associated with a higher incidence of chronic lung disease among survivors'. This should reinforce our hesitancy.

The purists may argue that conclusions can only be drawn when all the data are available. I certainly accept the scientific logic of this attitude but I have a sneaking suspicion that by adhering to such august principles we are in danger of rediscovering the wheelbarrow.

What appears to be clear is that if surfactant therapy is given to babies of a reasonable size and in good condition at birth a good outcome should be expected. My view is that to administer this treatment to tiny, cold acidotic babies is to court disaster. For such babies we require to sit down and think again.

- 1 Collaborative Multicenter Study Group. Surfactant replacement therapy for severe neonatal respiratory distress syndrome: an international randomized clinical trial. *Pediatrics* 1988;82:683-91.
- 2 Collaborative European Multicentre Study Group. Factors influencing the clinical response to surfactant replacement therapy in babies with severe respiratory distress syndrome. *Eur J Pediatr* 1991;150:433-9.
- 3 Long W, Thompson T, Sundell H, et al. Effect of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. *J Pediatr* 1991;118:595-605.
- 4 Horbar JD, Soll RF, Schachinger M, et al. A European multicentre randomized controlled trial of high dose surfactant therapy for idiopathic respiratory distress syndrome. *Eur J Pediatr* 1990;140:416-23.
- 5 Morley CJ. Surfactant treatment for premature babies—a review of clinical trials. *Arch Dis Child* 1991;66:445-50.
- 6 McCord FB, Curstedt T, Halliday HL, et al. Surfactant treatment and incidence of intraventricular haemorrhage in severe respiratory distress syndrome. *Arch Dis Child* 1988;63:10-6.
- 7 Merritt TA, Hallman M, Berry C, et al. Randomized, placebo-controlled trial of human surfactant given at birth versus rescue administration in very low birth weight infants with lung immaturity. *J Pediatr* 1991;118:581-94.

### Commentary

I agree with Professor McClure. The time for surfactant therapy has arrived but he is right to encourage caution and scepticism about individual clinical trials. Some of the trials have enrolled highly selected groups of babies, for example only babies weighing more than 700 g, on a ventilator, in more than 60% oxygen, or who have no complications. The results are then interpreted as applying to all babies.

However, there is now the most impressive body of data in the history of neonatology from multicentre, double blind, placebo controlled, randomised trials showing that surfactant replacement therapy saves lives and reduces morbidity. Surfactant used for prevention or treatment has been shown to be both safe and effective.

Surprisingly, Professor McClure has suggested that extremely small, hypothermic, asphyxiated babies should be excluded from the trials. I'm not quite sure he believes that they 'might have been better left alone', particularly as this is just the baby 'who needs our help most but who is at the limit or is possibly beyond the range of our knowledge'. If we do not study such babies they will remain beyond our knowledge. Their extreme im-

maturity might suggest that they will not respond dramatically to surfactant treatment. However, we will never know if we do not enter them into appropriate trials.

It is very difficult to obtain enough data from extremely low birthweight babies because they are relatively rare. In consequence most studies only allude to the possible effects in this group. The following information is available from published randomised controlled trials about the effect of treating extremely low birthweight babies with surfactant.

In a multicentre randomised trial placebo or Exosurf (5 ml/kg) was given to 215 babies with birth weights of 500 to 699 g.<sup>1</sup> Treatment with Exosurf was associated with a significant improvement in oxygen requirement, persisting for three days. The incidence of pneumothoraces was significantly reduced from 25/109 (23%) to 11/106 (10%), and deaths from respiratory distress syndrome were significantly reduced from 26/109 (24%) to 15/106 (14%). The incidence of other complications was not altered except that pulmonary haemorrhage occurred significantly more frequently in the Exosurf treated babies at 12/106 (11%) compared with 2/109 (2%) for the controls.

A randomised trial compared calf lung surfactant administered at 90 mg in 3 ml either prophylactically (n=235) or as rescue treatment (n=244) to babies less than 30 weeks' gestation, with repeated doses as necessary.<sup>2</sup> It was shown that there was a highly significant reduction in mortality in the babies less than 26 weeks who were treated with surfactant prophylactically 21/85 (25%) compared with rescue treatment 33/72 (46%). The incidence of pneumothorax was also reduced in the babies less than 26 weeks treated prophylactically 6/85 (7%) compared with the group given rescue treatment 13/72 (18%). There was no other significant effect. There was no indication that prophylactic therapy caused such small babies any harm.

In the ten centre trial of ALEC prophylaxis to babies between 25 and 29 weeks' gestation, the neonatal mortality for babies of 25 to 26 weeks' gestation was reduced from 15/32 (47%) to 13/43 (30%).<sup>3</sup> The sample size was small and this 36% reduction in mortality failed to reach statistical significance. The effect of artificial surfactant was equivalent to babies being older by over one week of gestation.

These effects of surfactant treatment on extremely immature babies although relatively preliminary, are consistent. They show that surfactant treatment for these extremely low birthweight babies has important beneficial effects. The only adverse effect so far reported is pulmonary haemorrhage with Exosurf. This has not been reported so far with other surfactants, although many trials have excluded babies less than 700 g and the number of such tiny babies in the other trials is relatively small.

Surfactant treatment has not been shown to have much effect on brain haemorrhages and