Cerebral blood flow velocity changes after rapid administration of surfactant

Sir,—We enjoyed reading the paper by Dr Cowan et al.1 which we suspect was written in response to an earlier paper by ourselves.2 In this earlier study we found a number of problems in relating the findings to the conclusion of the authors. The rationale behind the study appears to be the finding of an increased incidence of severe intraventricular haemorrhage in one study of surfactant replacement.3 The authors do mention two other randomised trials which reported a reduction of intraventricular haemorrhage, to which one might add a further two trials (this review lists four studies, references 37-40, which demonstrate significant reduction in intraventricular haemorrhage after surfactant treatment). Large intraventricular haemorrhage (IVH) and IV have also been shown to be reduced in four studies (references 37, 39, 50, 51).

A meta-analysis involving 34 randomised controlled trials shows odds ratios (95% confidence intervals) for the effect of surfactant on intraventricular haemorrhage of 0.89 (0.73-1.07) for prophylaxis and 0.79 (0.64-0.97) for rescue studies.4 The body of scientific evidence points to a modest reduction of intraventricular haemorrhage after surfactant treatment.

The authors go on to say that the collaborative European multicentre study of Curosurf found a surprisingly high incidence (26%) of severe intraventricular haemorrhage, but they omit to say just how all these infants were, as they required mechanical ventilation in >60% oxygen within the first 15 hours of life.5 Indeed the control infants had a mortality rate in excess of 50%. The incidence of severe intraventricular haemorrhage in this study is less than that reported in at least three other studies6 (references 54, 58, 67) using rescue surfactant.

Many of the babies studied by Cowan et al. would not have fulfilled the criteria for the collaborative European multicentre study of Curosurf7 as they were treated up to the age of 72 hours. The authors do not say whether any of their infants suffered from severe asphyxia, although we are told that the infants had pancuronium and pethidine. It seems likely that these babies were extremely ill and in the discussion it is said that seven out of eight had poor or absent cerebral autoregulation.8 The authors correctly point out that there was a modest reduction in mean arterial pressure after giving surfactant and on looking at their results it would seem that in some infants mean arterial pressure and cerebral blood flow velocity (CBFV) actually increased. Levels of mean arterial pressure in the graphs all appear to be above 30 mm Hg which is a level at which the authors had previously noted an increase of cerebral blood flow.9 The authors do not state the rate of intraventricular haemorrhage in their babies nor demonstrate any relationship between the reduction in either mean arterial pressure or CBFV and the severity of intraventricular haemorrhage. CBFV may not reliably reflect cerebral blood flow (CBF) when heart rate, blood pressure, carbon dioxide tension, and cerebral vessel diameter may all be changing. CBF measured using 133 xenon clearance (G Greisen and A Bell, personal communication) and near infrared spectroscopy (DR Reynolds and AD Edwards, personal communication) shows no consistent change after Curosurf administration and is related to change in carbon dioxide tension.

The final paragraph of the discussion again suggests that there is a relationship between surfactant treatment and increase in intraventricular haemorrhage where in fact none exists. The reduction in intraventricular haemorrhage is in keeping with our two year follow up studies with Curosurf which show that 80% of treated survivors have normal development compared with 72% of control infants.10 We are aware of only one study which has looked at a slow continuous infusion of Curosurf compared with the currently recommended bolus instillation. In this pilot study the intraventricular haemorrhage was less and the duration of effect greatly shortened. (PW Nars and C Rudin, personal communication). Perhaps there is a need for larger randomised trials of different methods of surfactant instillation in the haemorrhage and the dynamic changes reported by the authors were due to compromise of their infants before treatment or to their concomitant drug treatment.

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8 Dr Cowan et al comment: We appreciate the interest in our paper expressed by Drs Halliday and Robertson. Nowhere in our paper do we state that a consistent association had been shown between surfactant and intraventricular haemorrhage (IVH). While a number of randomised trials have shown a reduction in IVH, Horbar's multicentre trial with 106 infants randomised (unpublished) have a number of infants treated in infants developed severe (grade 3 or 4) IVH against 15-4% in the control group (p<0.01). In the collaborative European multicentre study of Curosurf slightly more infants developed severe IVH in the surfactant group than in the control group (no statistical significance).11 As surfactant treatment has consistently been shown to lower mortality it is extremely important to ensure that this is not at the expense of increased survival of infants brain damaged or with cerebral infarction. Thus we felt that more investigation of the changes in the cerebral circulation with bolus surfactant administration was needed.

All the infants we studied would have qualified for the collaborative multicentre study of Curosurf on all criteria. The infants were extremely ill, but these are precisely the infants most at risk of cerebral haemorrhage, and therefore the physiological changes are most important. Pancuronium and pethidine were used to prevent "fighting the ventilator". These two drugs are known to have a stabilising effect on blood pressure. Thus it is difficult to follow the suggestion that the haemodynamic changes could be due to these two drugs rather than the surfactant. We did not relate changes in blood pressure to scan findings and so too small a sample for statistical significance. We agree that velocity measurements may not always reflect flow but our findings of a change in a spectral pattern to one with low or absent peak and diastolic velocity suggests changes in flow pattern that may not be detectable by the other methods cited. We look forward to reading about the effects of slow continuous infusion of Curosurf.


Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia

Sir,—We read with interest the recent paper by Dr Ng and colleagues1 and would like to add a comment on prostaglandins. The authors did not refer to gastric prostaglandins in patients and prophylactic regimens in maternal breast milk, but these substances may play an important part in the aetiology and treatment of gastroduodenal mucosal lesions and perforation in preterm babies treated with dexamethasone. Prostaglandins, and PGE2 and PGI, in particular, are known to regulate protective factors in the gastroduodenal mucosa such as mucosal blood flow, mucus production, and bicarbonate secretion. An increase in prostaglandins in the gastroduodenal mucosa will therefore result in the depression of the protective mechanisms, thereby contributing to the development of gastroduodenal mucosal lesions. On the other hand, glucocorticosteroids are known to inhibit prostaglandin biosynthesis through the suppression of phospholipase A2 activity. Nobuhara et al have shown that cortisone acetate increases PGE2 and 6 keto PGI, in the gastric mucosa and have demonstrated a good correlation between this decrease and the development of gastric mucosal lesions.2 We have also demonstrated...