Cerebral blood flow velocity changes after rapid administration of surfactant

Sir,—We enjoyed reading the paper by Dr Cowan et al. who have 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.1 The authors do mention two other randomised trials which reported a reduction of intraventricular haemorrhage, to which one might add another two3,4 (this review lists four studies, references 37–40, which demonstrate significant reduction in intraventricular haemorrhage after surfactant treatment). Large intraventricular haemorrhage and IV have also been shown to be reduced in four studies5 (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.6 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 ill these infants were, as they required mechanical ventilation in >60% oxygen within the first 15 hours of life.1 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 studies7 (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 Curosurf8 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 panceurinomy and pethidine. It seems likely that these babies were extremely ill and in the discussion is it said that seven out of eight had poor or absent cerebral autoregulation.1 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 with 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.8 The authors do not discuss 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 (DRR 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 of 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.1 We have published 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 improvement in blood gases 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. It is perhaps the haemodynamic changes reported by the authors were due to compromise of their infants before treatment or to their concomitant drug treatment.

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Gastrodouenoidal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia

Sir,—We read with interest the recent paper by Dr Ng and colleagues9 and would like to add a comment on prostaglandins. The authors did not refer to gastric prostaglandins in patients and preterm infants in maternal breast milk, but these substances may play an important part in the aetiology and treatment of gastroduenoidal mucosal lesions and perforation in preterm babies treated with dexamethasone. Prostaglandins, and PGE2 and PGI2 in particular, are known to regulate protective factors in the gastroduenoidal mucosa such as mucosal blood flow, mucus production, and bicarbonate secretion. An increase in prostaglandins in the gastroduenoidal mucosa will therefore result in the depression of the protective mechanisms, thereby contributing to the development of gastroduenoidal 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 prostaglandins protect the gastric mucosa and have demonstrated a good correlation between this decrease and the development of gastric mucosal lesions.2 We have also demonstrated

an impaired increase in PGE2 in gastric juices which is thought to reflect the amount of PGE2 in the gastric mucosa during steroid treatment in children. Moreover, Marino et al have reported that the PGE2 concentration in the gastric secretion in premature infants was significantly lower than that in full term infants. 4 On the basis of these findings we suggest that a decrease or impaired increase in PGE2 in the gastroduodenal mucosa is one of the important factors in the development of gastroduodenal mucosal lesions and perforation in preterm babies treated with dexamethasone.

This suggestion may have a therapeutic implication when it comes to breast feeding, although Ng et al described it in only one of four cases, the administration of oral PGE2 analogues has been shown to protect the gastric mucosa from steroid induced damage. 5 In addition, a considerable quantity of prostaglandins including PGE2 has been identified in human milk but not in infant formula. 6 Consequently, breast feeding may have an important protective effect on gastroduodenal mucosal lesions in preterm infants during steroid treatment.

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The prophylactic use of ranitidine in babies treated with dexamethasone

Str,—The Collaborative Dexamethasone Trial Group recently reported an increase in gastrointestinal bleeding among dexamethasone treated preterm infants compared with controls, although this did not reach statistical significance. 1 This trial did not report any babies with gastrointestinal perforation but two recent papers in this journal estimated an incidence of perforation of the order of 2-3%, and it was associated with considerable morbidity and mortality. 2, 3

The mechanism by which steroids cause gastrointestinal ulceration is unclear, although it is generally accepted that they reduce the effectiveness of the protective mucosal barrier. In this situation normal acid production may be sufficient to cause gastrointestinal perforation. Since we noted this complication we have assessed gastric acid production, with the H2 receptor antagonist ranitidine, in all babies treated with steroids. To determine the effectiveness of this practice we have been serially monitoring gastric pH in babies treated with dexamethasone and various doses of ranitidine.

We report the results of using a ranitidine infusion of 0.0625 mg/kg/hour in seven babies treated with dexamethasone and not receiving enteral feeding. Patient characteristics and results are presented in the table. This dose of ranitidine caused a significant increase in gastric pH (p<0.0001).

In order to test whether or not the routine use of an H2 antagonist would significantly reduce the incidence of gastrointestinal bleeding or perforation due to dexamethasone a controlled trial in more than 2000 babies would have to be performed. Although this would be desirable, as it would allow adverse as well as beneficial effects to be looked for, it is unlikely to be done. In the meantime, because of its demonstrated effectiveness in reducing gastric acid secretion, we currently administer ranitidine prophylactically to all babies treated with dexamethasone.
Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia.

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