Cerebral blood flow velocity changes after rapid administration of surfactant

Sr.—We enjoyed reading the paper by Dr Cowan et al, which has 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. The authors do mention two other randomised trials which reported a reduction of intraventricular haemorrhage, to which one might add a further two (this review lists four studies, references 37–40, which demonstrate significant reduction in intraventricular haemorrhage after surfactant treatment). Large intraventricular haemorrhage III 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. The body of scientific evidence points to a modest reduction in 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. 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 studies (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 Curosurf 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. 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, since 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 lesions. 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 (IVH). 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 exist. 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. We are aware of only one study which has looked at a slow continuous infusion of Curosurf compared with the currently recommended bolus installation. In this pilot study Curosurf was infused at a slower rate than the KaVo catheter 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 and 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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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 has been shown between intraventricular haemorrhage (IVH) and cerebral blood flow velocity (CBFV) actual increases in 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. While a number of randomised trials have shown a reduction in IVH, Horbar's multicentre trial with 106 infants randomised to one of 3 treatments have a number of infants treated in infants developed severe grade 3 or 4 IVH at a rate of 15%–45% 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). 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 with brain damage, particularly periventricular leucomalacia. Thus we felt that more investigation of the changes in the cerebral circulation with bolus surfactant administration was needed.

All the infants we studied had 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 lesions and therefore much more likely to benefit from surfactant treatment. 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 justify further research as 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 as the too small number of scans is insufficient 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 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.

St. 


Gastrointestinal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia

Sr.—We read with interest the recent paper by Dr Ng and colleagues1 and would like to add a comment on prostanoids. The authors did not refer to gastric prostanoids in patients and preterm babies treated with dexamethasone. Prostaglandins, and PGF2α and PGE2 in particular, are known to regulate protective factors in the gastric mucosa such as mucosal blood flow, mucus production, and bicarbonate secretion. Inhibition of prostanoids 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 prostanoid biosynthesis through the suppression of phospholipase A2 activity. Nobuhara et al have shown that in rat larvae slices, PGE2 and 6- keto PGF2α 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
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 and colleagues have reported that the PGE₂ concentration in the gastric secretion in premature infants was significantly lower than that in full-term infants. On the administration of oral PGE₂ analogues has been shown to protect the gastric mucosa from steroid induced damage. In addition, a considerable quantity of prostaglandins including PGE₂ has been identified in human milk but not in infant formula. 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. 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. 1

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 used ranitidine acid suppression, with the H₂ receptor antagonist ranitidine, in all babies treated with steroids. To determine the effectiveness of this practice we have been serially determining 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<0.001).

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 involving 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.

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Non-invasive assessment of pulmonary arterial pressure in healthy neonates

Str,—Recent correspondence in this journal referred to the assessment of pulmonary artery pressure by Doppler using the ratio of time to peak velocity (TPV) : right ventricular ejection time (RVET). 1 We should like to point out that the position of the regression line relating TPV:RVET to pulmonary artery pressure is influenced by whether the pulsed Doppler sample is taken from the right ventricular outflow tract proximal to the pulmonary valve or from the main pulmonary artery. If TPV:RVET, measured from the main pulmonary artery, is plotted on a regression line derived from measurements made in the right ventr-
cular outflow tract then an inappropriately high mean pulmonary artery pressure will be obtained. This explains why Skinner et al, commenting on our letter, 2 found an impos-
sibly high pulmonary artery pressure of 100 mm Hg when they plotted our measurement of TPV:RVET (sampled from main pulmonary artery) on a regression line based on Kitabatake’s measurements (sampled from right ventricular outflow tract). 2

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1 Evans N, Archer N. Non-invasive assessment of pulmonary arterial pressure in healthy neo-


Respiratory support using patient triggered ventilation in the neonatal period

Str,—I should like to comment on your recent timely article on patient triggered ventilation in the neonatal period. 1 The authors indicate that a recent study patient triggered vential-
fation (PTV) was successful only in three out of 16 infants with chronic lung disease because of asynchrony or poorly sustained respiratory effort in these infants. It may be more appropriate to use a longer inspiratory time (0-6 seconds) when ventilating these babies in trigger mode as this has been shown to be associated with an increase in tidal volume due to recruitment of more collapsed alveoli. 2 Similarly, if such an infant is being weaned using PTV, doing so by decreasing peak inspiratory pressure may result in progressive alveolar collapse. We have recently had difficulties weaning an infant with chronic lung disease in this way. PTV using a ventilator with a built in refractory period resulting in inactivation of the trigger for some of the babies own breaths enables peak inspiratory pressure and inspiratory time to be maintained and might be more appropriate for weaning infants with chronic lung disease.

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Is 28 weeks gestation equivalent to 1000 g of birth weight?

Str,—With the rapid development of neonatal intensive care, many tiny and premature babies are now surviving. In 1979 the World Health Organisation published a number of recommendations on the methodology of reporting perinatal mortality statistics. 1 It is recommended that countries should present, solely for international comparisons, “standard perinatal statistics” in which both the numerator and denominator of all rates are restricted to fetuses and infants weighing more than 400 grams (or, where birthweight is unavailable, the corresponding gestational age (28 weeks) or body length (35 cm crown-heel)). These recommendations have been strongly endorsed by the International Federation of Gynecolo-
isticians and Obstetricians. 2 In the 9th revision of the International Classification of Diseases Clinical Modification, 3 extreme immaturity (code 765.0) is defined as ‘Usually implies a birthweight of less than 1000 grams and/or a gestation of less than 28 completed weeks’, and other preterm infants (code 765.1) as ‘Usually implies a birthweight of 1000–2499 grams’. 4

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