LETTERS TO THE EDITOR

Cerebral blood flow velocity changes after rapid administration of surfactant

SIR,—We enjoyed reading the paper by Dr Cowan *et al.*¹ but we 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.² The authors do mention two other randomised trials which reported a reduction of intraventricular haemorrhage, to which one might add a further two³ (this review lists four studies, references 37-40, which demonstrate significant reduction in intraventricular haemorrhage after surfactant treatment). Large intraventricular haemorrhages of grade III and IV have also been shown to be reduced in four studies³ (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 ill 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 studies³ (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 Curosurf⁵ 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.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 velocities (CBFV) actually increased. The 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.⁶ The authors do not report 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 (EOR 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.⁷ 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 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 or perhaps the haemodynamic changes reported by the authors were due to compromise of their infants before treatment or to their concomitant drug treatment.

HENRY HALLIDAY
Department of Child Health,
Institute of Clinical Science,
The Queen's University of Belfast,
Grosvenor Road, Belfast BT12 6BB

BENGT ROBERTSON
Research Unit for Experimental
Perinatal Pathology,
St Goran's Hospital,
S-112 81 Stockholm,
Sweden

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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 surfactant treatment and intraventricular haemorrhage (IVH). While a number of randomised trials have shown a reduction in IVH, Horbar's multicentre trial with 106 infants randomised found 38.5% of surfactant treated in infants developed severe (grade 3 or 4) IVH against 15.4% in the control group ($p < 0.01$).¹ 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).² 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 by haemorrhage or ischaemia. 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 lesions and where physiological information is needed. Pancuronium and pethidine were used to prevent 'fighting the ventilator'. These two drugs are known to have a stabilising effect on blood pressure.³ 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 as the numbers were too small for statistical significance. We agree that velocity measurements may not always reflect flow but our findings of a change in spectral pattern to one with low or absent end 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.

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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 prostaglandins 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 PGI₂ in particular, are known to regulate protective factors in the gastroduodenal mucosa such as mucosal blood flow, mucus production, and bicarbonate secretion. A decrease 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 prednisolone reduces PGE₂ and 6-keto PGF_{1α} 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.³ 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.² In addition, a considerable quantity of prostaglandins including PGE₂ has been identified in human milk but not in infant formulas.⁵ Consequently, breast feeding may have an important protective effect on gastroduodenal mucosal lesions in preterm infants during steroid treatment.

TOSHIAKI SHIMIZU
YUICHIRO YAMASHIRO
KEIJIRO YABUTA
Department of Paediatrics,
University of Juntendo,
2-1-1 Hongo Bunkyo-ku Tokyo,
Japan

- 1 Ng PC, Brownlee KG, Dear PRF. Gastro-duodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991;66:1164-6.
- 2 Nobuhara Y, Ueki S, Takeuchi K. Influence of prednisolone on gastric alkaline response in rat stomach: a possible explanation for steroid-induced gastric lesion. *Dig Dis Sci* 1985;30:1166-73.
- 3 Shimizu T, Shioya T, Yamashiro Y, Sato M, Yabuta K. Impaired increase of prostaglandin E₂ in gastric juice during steroid therapy in children. *J Pediatr Gastroenterol Nutr* 1991;13:326.
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The prophylactic use of ranitidine in babies treated with dexamethasone

SIR,—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 tried to reduce 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 effects of using a ranitidine infusion of 0.0625 mg/kg/hour in seven babies

The characteristics and results of the patients studied

	Gestation (weeks)	Weight (g)	pH before ranitidine	pH while on ranitidine
Mean	27.7	849	1.7	4.9
Range	24-31	579-1171	1.3-2.0	4.2-6.0

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 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.

E J KELLY
K G BROWNLEE
P C NG
P R F DEAR
Academic Unit of Paediatrics and Child Health,
St James's University Hospital,
Beckett Street,
Leeds LS9 7TF

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Non-invasive assessment of pulmonary arterial pressure in healthy neonates

SIR,—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 ventricular outflow tract then an inappropriately high mean pulmonary artery pressure will be obtained. This explains why Skinner *et al*, commenting on our letter,¹ found an impossibly 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

NICK EVANS
NICK ARCHER
Department of Paediatrics,
John Radcliffe Hospital,
Headington,
Oxford OX3 9DU

- 1 Evans N, Archer N. Non-invasive assessment of pulmonary arterial pressure in healthy neonates. *Arch Dis Child* 1991;66:1100.
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Respiratory support using patient triggered ventilation in the neonatal period

SIR,—I should like to comment on your recent timely article on patient triggered ventilation in the neonatal period.¹ The authors indicate that in a recent study patient triggered ventilation (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 difficulty 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.

N J SHAW
G A B RUSSELL
Department of Child Health,
Liverpool Maternity Hospital,
Oxford Street,
Liverpool L7 7BN

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

SIR,—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 statistics¹: '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 1000 g or more (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 Gynecologists 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