LETTERS TO THE EDITOR

Double blind trial of recombinant human erythropoietin in preterm infants

EDITOR,—A recent paper demonstrates very clearly the dangers of allowing those who may benefit financially from the results of a study to be involved in reporting that study. The double blind trial of recombinant human erythropoietin (r-HuEpo) in preterm infants reported by Emmerson, *et al* was supported by Cilag Ltd.¹ The r-HuEpo used was supplied by Cilag Ltd and one of the authors is employed by Cilag Ltd.

The abstract of the paper outlines the form of the double blind study. It reports a significant rise in the reticulocyte count in the r-HuEpo group, and a reduction in the number of transfusions needed compared with the placebo group, and some differences in haematological indices. The abstract concludes: 'The study provides strong evidence for the efficacy of r-Hu-Epo in stimulating erythropoiesis and reducing the requirement for transfusions for anaemia of prematurity'.

I suspect I was not alone in at first accepting that abstract at face value. It was only on reading the whole paper that I discovered that the abstract is dangerously misleading. In fact there was no significant difference in the proportions of each group requiring transfusion, there was no significant difference in the mean volume of blood transfused in each group, and at no time during the study or three months' follow up was there any significant difference in mean haemoglobin concentration between the two groups.

By far the most misleading aspect of the abstract, however, was the failure to mention that 20% of the r-Hu-Epo group died within a month of the end of the trial, while no infant in the placebo group died. Three out of 15 infants receiving r-HuEpo while in hospital died within four weeks of being discharged home, one from volvulus and gut infarction, and two from sudden infant death syndrome (SIDS). Whether one looks at the incidence of SIDS, or more general figures of mortality in preterm infants, the odds against three such deaths happening by chance in a group of 15 infants are several thousands to one.

Such deaths should surely have resulted in very obvious warnings, in the abstract and elsewhere, about an as yet unexplained potential danger of r-HuEpo. Instead the authors are dismissive of the danger, and conclude that: 'further studies with larger numbers of infants are required to clarify the optimal dose, frequency, and starting time for the prevention of this anaemia'.

Your publication of this paper raises several questions that require answers:

- (1) Do the authors have any better reasons than those so far presented for believing that the deaths were not linked to r-HuEpo, when statistically it is highly likely that they were?
- (2) Why have the deaths not been reported to the Committee on Safety of Medicines?
- (3) Can the authors rebut the inevitable suspicion that the abstract was framed in such a way as to protect Cilag Ltd's commercial interests?

(4) How did the paper and its abstract manage to pass the peer review and editorial processes?

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- 1 Emmerson AJB, Coles HJ, Stern CMM, Pearson TC. Double blind trial of recombinant human erythropoietin in preterm infants. *Arch Dis Child* 1993; 68: 291-6.

Dr Emmerson comments:

The deaths of the infants in the clinical trial of r-HuEpo in preterm infants are a concern shared by many, not least by the authors of the paper, however that this should lead to very obvious warnings in the abstract is strongly refuted.

It is inappropriate to group the three deaths together. One of the deaths was an infant who developed an acute volvulus of the gut after cessation of treatment, and this was a clear cause of death. Of more concern are the two infants who died from SIDS, four weeks after stopping treatment, both having received different r-HuEpo doses. Statistically the chance of two infants dying of SIDS within one group of 15 infants is small, but this does not confirm a causal relationship.

No attempt was made to mislead the reader. Throughout the paper there is open discussion of these deaths, including in the subjects and methods section where the premature termination of the study was reported. This demonstrates that the authors took these deaths extremely seriously, feeling it inappropriate to continue the double blind trial without breaking the code and analysing the data. In addition to very careful scrutiny of the data for the whole group and for the two SIDS infants, an extensive search of the world experience (published and unpublished) was made for other cases. No other cases of SIDS have occurred with the use of r-HuEpo. The doses employed in some other studies have been several times higher, and taking this and the numbers treated in all studies the significance of the possible association of SIDS and r-HuEpo is reduced.¹⁻³ These points are made clearly in the paper. Theoretical mechanisms whereby r-HuEpo may have resulted in SIDS are given in the discussion, and the whole approach of the paper cannot be considered to be dismissive of the danger.

The authors did not feel that a warning of the dangers of using r-HuEpo in preterm infants was appropriate, for the reasons stated above, and in that respect it was not recorded in the abstract which, being a brief summary, should in no way replace reading the full paper.

The authors take strong exception to the suggestion that Cilag's commercial interests influenced the publication. The inclusion of the author from Cilag Ltd, a senior clinical research associate, acknowledged her contribution to the monitoring and conductance of this study ensuring adherence to good clinical practice.

Dr Nicholson's question relating to the reporting of the deaths to the Committee on Safety of Medicines is unfounded as all the deaths were promptly reported (as is the legal requirement) between two and 10 days after death.

All the authors agree that it is essential to have proper reporting of adverse events, but to have over interpreted the possible association of SIDS and the use of r-HuEpo in the absence of any other evidence to support it

would have been incorrect and irresponsible.

The authors maintain the view that there was appropriate consideration and reporting of the data and that the correct balance between the data in the abstract and the whole paper was made.

- 1 Carnielli V, Montini G, Da Riò R, Dall'Amico R, Cantarutti F. Effect of high doses of human recombinant erythropoietin on the need for blood transfusions in preterm infants. *J Pediatr* 1992; 121: 98-102.
- 2 Shannon KM, Mentzer WC, Abels RI, *et al*. Enhancement of erythropoiesis by recombinant human erythropoietin in low birth weight infants: a pilot study. *J Pediatr* 1992; 120: 586-92.
- 3 Ohls RK, Christensen RD. Recombinant erythropoietin compared with erythrocyte transfusion in the treatment of anaemia of prematurity. *J Pediatr* 1991; 119: 781-8.

Antenatal assessment of neurological impairment

EDITOR,—We write to criticise the management of a 23 year old primigravida with a varicella infected fetus reported by Taylor *et al*.¹ Their stated purpose is to illustrate that antenatal assessment can offer insight into the ultimate prognosis of the infant. However, it is possible that the authors miss the point.

The mother presented at 27 weeks for decreased fetal movements. The fetus exhibited a markedly fixed fetal heart rate pattern. The primary care centre appropriately referred her to a maternal fetal centre.

The consultants gathered every piece of data to reach the exact diagnosis. Varicella IgM was present in fetal blood. Fetal blood showed normoxia and normal acid base balance. The occurrence of a fixed fetal heart rate pattern with normoxia and normal pH has been well described in the literature as being consistent with fetal brain death.²⁻⁴ The differential diagnosis of a fixed fetal heart rate is limited, including: fetal quiet sleep (fetal behavioural state IF), maternal drug ingestion (diazepam, pethidine), and anencephaly. Fetal quiet sleep is excluded simply by extending the fetal heart recording to at least 60 minutes. Fetal drug ingestion is confirmed by history and anencephaly is, of course, diagnosed by ultrasound.

This fetus never had sustained breathing movements, and polyhydramnios developed.

After this elegant evaluation one would expect state of the art management. What follows is most surprising: (1) conservative management 'in the absence of evidence of hypoxaemia'; (2) 'elective caesarean section at 39 weeks because of the difficulty of monitoring a fetus with an unvarying heart rate'; and (3) extremely aggressive paediatric management of a severely damaged child. Therefore, in spite of a correct diagnosis of congenital varicella zoster infection with hepatic and brain stem involvement the fetus and subsequently the infant were managed aggressively. The child lived for 10 months with a tracheostomy, fundal plication, gastrostomy, and ligation of the patent ductus arteriosus.

The discussion reviews the elements necessary to assess fetal distress, yet never mentions 'fetal brain death'.

There are excellent data in the European obstetric literature showing that a non-variable fetal heart rate accompanied by normoxia and normal acid base balance is consistent with fetal brain death; in such cases caesarean section must be avoided. If the consultants had made the diagnosis of fetal brain death, the unnecessary caesarean