Double blind trial of recombinant human erythropoietin in preterm infants

Dr Emmerson comments:

The deaths of the infants in the clinical trial of r-HuEpo in preterm infants are, I believe, 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 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 sepsis in the following 2 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 variability in the survival of the infants for the whole group and for the two SIDS infants, an extensive search of the world experience (published and unpublished) was made for other cases.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 this event is most unlikely. The authors have emphasized that the deaths are severe, and no one can claim that the deaths are not severe.

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 and to the authors is relevant. In this case 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?

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

LETTERS TO
THE EDITOR


Antenatal assessment of neurological impairment

Dr Emmerson—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. The r-HuEpo 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 reticuloocyte 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-HuEpo in stimulating erythropoiesis and reducing the requirement for transfusions for anaemia of prematurity'.

I suspect I was not alone in first accepting this 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-HuEpo group died within a month of the end of the trial, whereas one in five of the infants 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 one 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 threat to the outcome of the trial. 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 transfusion.'

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 process?

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section and costly (financial and emotional) care of this infant could have been avoided.

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Mr Taylor and Mr Walkinshaw comment:

We are aware of the case report literature on fetal brain death, almost all of which is secondary to known severe hypoxia.1 In our case we aimed to illustrate cranial nerve defects, and our dynamic ultrasonic findings evolved over several weeks. There was no evidence from the history or later postmortem examination to suggest an anoxic insult. The confirmation of fetal varicella IgM antibodies was delayed for several weeks. Local laboratory testing was negative, but referral to the Manchester PHSL Reference Laboratory gave the reported result. The cardiotocograph (fig. 1) does not fulfil the criteria for fetal brain death. The baseline was inappropriate for the gestation and close scrutiny of the illustration reveals shallow decelerations.1 We accept, however, that this should have been elaborated on in our discussion.

Lessons are being learned from anatomical prenatal diagnosis and false positive diagnoses illustrate its lack of precision. We would urge caution in the new field of functional diagnosis rather than to take a didactic approach. We are not aware of any reported literature on how often a potential false positive diagnosis of fetal brain death is made. Even a biophysical profile score of 2 before delivery is not always associated with a poor neonatal outcome.2 We felt after discussion with the parents that the death should be given the benefit of these doubts.

The paediatric management was aggressive and reflected the reluctance of the paediatricians to accept the reliability of a functional diagnosis. The obstetric authors (WGT, SAW) agree with Sheila Gahagan and Claudine Amiel-Tison that some of the paediatric investigations and management was unnecessary.


When will my baby go home?

EDITOR.—Powell et al report that parents of preterm babies frequently ask: when will my baby go home?1 This question is often asked in the Netherlands as well. In the study cited by Powell et al as reporting mortality and morbidity only,2 we asked exactly that question. The results have been published in a Dutch language medical journal.3 Of the nationwide cohort of very preterm (gestational age less than 32 completed weeks) and (or) very low birthweight (less than 1500 g) infants the 992 surviving infants were discharged home after a mean hospital stay of 68 days (range 6-380 days).

For all infants, the difference was calculated between the expected date of delivery and the date of discharge. The figure shows the number of infants discharged per category of days before and after term. The distribution shows that, as in the study of Powell et al, many of these infants were discharged around 36 to 37 weeks’ postconceptional age (term minus 25 to minus 15 days). A total of 60% of all infants went home at or before 42 weeks’ postconceptional age. However, 10% of these very preterm infants were still in the hospital at five weeks after the expected date of birth. We concluded that for this category of preterm babies, the answer to the parents’ question should be: half of these babies can go home at or before the expected date of delivery, 70% are home two weeks after that, and 90% are home at five weeks after term.

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Bilateral congenital diaphragmatic hernia – delayed presentation of the contralateral defect

EDITOR.—Approximately 3% of congenital diaphragmatic defects are bilateral.1 Historically this condition has been almost uniformly fatal, with the first UK survivor reported in 1990.2 We have successfully treated two patients in whom diagnosis of the contralateral hernia was delayed.

Number of infants discharged at various ages in relation to term date (expected date of delivery) (n=992). (Figure adapted from Het Nederlands Tijdschrift voor Geneeskunde (1988; 132: 1667-8) and reproduced with permission.)