could obliterate transient configurational changes in the fetal ECG. In our study only the raw fetal ECG signal was examined, without the assistance of computer averaging techniques. Although this allowed the observation of transient configurational changes to be seen, many signals were unsatisfactory for analysis due to electrical noise interference. Vagal mechanisms are clearly involved in the production of sinus bradycardias and a change in pacemaker site. Excessive vagal activity may completely block the sinoatrial node producing the sick sinus syndrome. Complete atrioventricular block implies an interruption in the myocardial conduction system between the sinoatrial node (SAN) and the atrioventricular node (AVN). This is unlikely to be caused by a vagal mechanism, but rather, cellular hypoxia along the His bundle, an area of the conduction system known to be very sensitive to hypoxia.[7] Both the SAN and AVN are resistant to hypoxia and will continue to fire action potentials, albeit independently, despite low levels of oxygen.[7]

Severe variable decelerations of the fetal heart rate have been more often associated with abnormalities of fetal acid base,[8] as have absolute degrees of deceleration,[9] which would support this phenomenon of atrioventricular heart block.

Techniques which permit accurate evaluation of the fetal ECG during labour may assist in the differentiation between bradycardias caused by vagal reflex activity and the more sinister conduction defects attributable to asphyxia.

1 von Winckel F. Lehrbuch der Geburtshulfe einschliesslich der Pathologie und Therapie des Wochenbetts. *Fur praktische Aerzte und Studierende 2.* Aufl. Leipzig, Veit, 1893.
2 Hon EH. Observations on pathological fetal bradycardia. *Am J Obstet Gynecol* 1959; **77:** 1084.
3 Pardi G, Tucci E, Uderzo Z, Zanini D. Fetal electrocardiogram changes in relation to fetal heart rate patterns during labour. *Am J Obstet Gynecol* 1974; **118:** 243–50.
4 Hon EH, Bradfield AH, Hess OW. The electronic evaluation of the fetal heart rate. V The vagal factor in fetal bradycardia. *Am J Obstet Gynecol* 1961; **82:** 291–300.
5 Yeh M-N, Moroshima HO, Niemann WH, James LS. Myocardial conduction defects in association with compression of the umbilical cord. *Am J Obstet Gynecol* 1975; **121:** 951–7.
6 Reeves JT, Daoud FS, Eastin C. Effect of vagotomy on arterial blood pressure and blood gases in the fetal calf. *Am J Physiol* 1971; **221:** 349.
7 James TN, Sherf L, Fine G, Morales AR. Comparative ultrastructure of the sinus node in man and dog. *Circulation* 1966; XXXIV: 139–60.
8 Beard RW, Filshie GM, Knight CA, Roberts GM. The significance of the changes in the continuous fetal heart rate in the first stage of labour. *J Obstet Gynaecol Br Commonwealth* 1971; **78:** 865–81.
9 Tipton RF, Finch AJ. The measurement and significance of transient fetal bradycardia during labour. *J Obstet Gynaecol Br Commonwealth.* 1972; **79:** 133–4.

Granulocyte colony stimulating factor treatment for neonatal neutropenia

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Abstract

In a pilot study recombinant human granulocyte colony-stimulating factor (rhG-CSF) was administered to 12 neutropenic preterm infants to determine if neonatal neutropenia is secondary to decreased endogenous G-CSF production. Respiratory variables were monitored because of the possible link between inflammatory cells and hyaline membrane disease. All infants showed increased neutrophil counts. The only possible side effect observed was an exacerbation of thrombocytopenia.

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Keywords: neonatal neutropenia, treatment, rhG-CSF.

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Neutropenia occurs frequently in preterm infants and, when associated with sepsis, mortality is high.[1] Recombinant human granulocyte colony stimulating factor (rhG-CSF) induces significant neutrophilia and neutrophil storage pool proliferation in non-neutropenic[2] and neutropenic[3] neonates, without toxicity.

The effect of rhG-CSF in 12 critically ill neutropenic neonates was evaluated. Respiratory variables were particularly monitored because inflammatory cells or mediators may be involved in the pathogenesis of hyaline membrane disease and its sequelae.[4] Pre-treatment G-CSF concentrations were measured to investigate the hypothesis that neonatal neutropenia is secondary to decreased endogenous G-CSF production.[5]

Methods

RhG-CSF was administered if: (i) absolute neutrophil count (ANC) was $\leq 2\times10^9$/l with suspected infection; or (ii) ANC was $\leq 1\times10^9$/l and the infant was receiving intensive care. Diagnosis of infection was subsequently confirmed if: a pathogen was cultured from a nor-

Table 1 Details of infants studied showing median (range) of values

Birth weight (kg)	0·88 (0·65–2·2)
Gestational age (weeks)	28 (24–35)
Postnatal age (days)	3 (1–45)
Days of treatment	4 (1–8)
Pre-treatment plasma G-CSF (pg/ml)	3112 (60–25000)*

*Normal range for adults <100 pg/ml.

Table 2 Median (range) haematological variables before and after rhG-CSF treatment

Absolute counts	*Before treatment*	*Peak after treatment*	*p Values*
Neutrophils $\times 10^9$/l	0·7 (0·1–1·2)	6·6 (0·8–61)	<0·01
Monocytes $\times 10^9$/l	0·3 (0·1–1·7)	1·1 (0·3–14·3)	<0·01
Platelets $\times 10^9$/l	150 (53–235)	46 (19–113)	<0·01

mally sterile body site; new chest radiograph abnormality was accompanied by a pure growth of organisms in endotracheal tube secretions; or necrotising enterocolitis with pneumatosis intestinalis occurred. 'Probable infection' occurred if negative cultures accompanied clinical signs of sepsis.

Parents gave written informed consent in accordance with District Ethics Committee approval.

Pre-treatment plasma samples (0·5 ml) were obtained for measurement of endogenous G-CSF by commercial enzyme linked immunosorbent assay (ELISA). RhG-CSF (Filgrastim; Amgen Roche) 5 μg/kg/daily was administered intravenously until a response occurred (ANC of $\geq 5 \times 10^9$/l) for five days. In the absence of response the dose was increased to 10 μg/kg/daily for a further five days. Arterial full blood counts, blood gases, vital signs and ventilatory requirements were monitored. Blood films were inspected microscopically and results analysed using the Wilcoxon signed rank test.

Results

Clinical details, pre-treatment endogenous G-CSF, and cell counts are shown in tables 1 and 2. All patients received appropriate antibiotics and all required respiratory support. Infection was confirmed in seven and probable infection occurred in two. No infection was evident in three babies born to hypertensive mothers. Six infants survived. One subsequently sustained sudden infant death but five infants remain healthy with no further episodes of neutropenia or sepsis at the time of writing. Two infants had overwhelming septicaemia before receiving rhG-CSF and died within hours of its administration. Four others died of pre-existing severe respiratory disease. There was no evidence that rhG-CSF had an adverse affect on the respiratory variables monitored.

Discussion

In all infants ANC increased in response to rhG-CSF after a median of four days. In adults an increase in circulating ANC after a single dose correlates with marrow cellularity.[6] This implies that haematopoietic tissue in those babies requiring more than one dose of rhG-CSF was hypocellular and a 'true' response on neutrophil production was seen. In all but one infant endogenous G-CSF were grossly increased, yet the treatment resulted in a neutrophil response. This suggests that resistance of neutrophil progenitors to endogenous G-CSF action, rather than defective G-CSF production,[5] may have contributed to neutropenia.

Thrombocytopenia was a possible complication of treatment and has not been reported before.[1 2] However, platelet count was decreasing before rhG-CSF administration in all infants, and other recognised causes of thrombocytopenia coexisted – for example, infection and maternal hypertension. No evidence of respiratory complications was identified but this could not be conclusively evaluated in this pilot study.

In conclusion, rhG-CSF increased ANC in 12 critically ill infants and may have contributed to survival in six. The treated infants were extremely compromised and so therapeutic intervention was less likely to prevent fatality. Immediate toxicity was not evident but thrombocytopenia may have been exacerbated. A placebo controlled trial is required to assess the potential benefits and risks of rhG-CSF treatment in neonates at high risk of sepsis.

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1 Rodwell RL, Faims PHD, Taylor KMCD, Tudehope DI, Gray PH. Hematologic scoring system in early diagnosis of sepsis in neutropenic newborns. *Pediatr Infect Dis J* 1993; **12:** 372–6.
2 Gillan E, Yu S, Stringham D, Ellis R, Hunter D, Christensen R, *et al.* A randomised placebo-controlled phase I/II trial of rhG-CSF in newborns with presumed sepsis: absence of toxicity and induction of significant neutrophilia and bone marrow storage and progenitor pools. *Pediatr Res* 1993; **33:** 291.
3 Roberts RL, Szelc CM, Scates SM, Boyd MT, Soderstrom KM, Davis MW, *et al.* Neutropenia in an extremely premature infant treated with recombinant human granulocyte colony-stimulating factor. *Am J Dis Child* 1991; **145:** 808–12.
4 Ogden BE, Murphy SA, Saunders GC, Pathak D, Johnson JD. Neonatal lung neutrophils and elastase/proteinase inhibitor imbalance. *Am Rev Respir Dis* 1984; **130:** 817–21.
5 Cairo M. Therapeutic implications of dysregulated colony-stimulating factor expression in neonates. *Blood* 1993; **82:** 2269–72.
6 Hansen PB, Johnsen HE, Ralfkiaer E, Hansen NE. Blood neutrophil increment after a single dose of rhG-CSF or rhGM-CSF correlates with marrow cellularity and may predict the grade of neutropenia after chemotherapy. *Br J Haematol* 1993; **84:** 581–5.