could oblit rate transient configurational changes in the fetal ECG. In our study only the raw fetal ECG signal was examined, without the assistance of computer averaging tech niques. 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 brady cardias and a change in pacemaker site. Excessive vagal activity may completely block the sionatrial node producing the sick sinus syndrome. Complete atrioventricular block implies an interruption in the myocardial conduction system between the sionatrial 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. Both the SAN and AVN are resistant to hypoxia and will continue to fire action potentials, albeit independently, despite low levels of oxygen.

Severe variable decelerations of the fetal heart rate have been more often associated with abnormalities of fetal acid base, as have absolute degrees of deceleration, 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.


Granulocyte colony stimulating factor treatment for neonatal neutropenia

Alison R Bedford Russell, E Graham Davies, Sarah E Ball, Edward Gordon-Smith

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.

Neutropenia occurs frequently in preterm infants and, when associated with sepsis, mortality is high. Recombinant human granulocyte colony stimulating factor (rhG-CSF) induces significant neutrophilia and neutrophil storage pool proliferation in non-neutropenic and neutropenic neonates, without toxicity. The effect of rhG-CSF in 12 critically ill 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. Pre-treatment G-CSF concentrations were measured to investigate the hypothesis that neonatal neutropenia is secondary to decreased endogenous G-CSF production.

Methods
RhG-CSF was administered if: (i) absolute neutrophil count (ANC) was $\leq 2 \times 10^9/l$ with suspected infection; or (ii) ANC was $< 1 \times 10^9/l$ and the infant was receiving intensive care. Diagnosis of infection was subsequently confirmed if: a pathogen was cultured from a nor-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Details of infants studied showing median (range) of values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td>0.88 (0.65-2.2)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>28 (24-35)</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
<td>3 (1-45)</td>
</tr>
<tr>
<td>Days of treatment</td>
<td>4 (1-8)</td>
</tr>
<tr>
<td>Pre-treatment plasma G-CSF (pg/ml)</td>
<td>3112 (50-25000)*</td>
</tr>
</tbody>
</table>

*Normal range for adults < 100 pg/ml.

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mally sterile body site; new chest radiograph abnormality was accompanied by a pure growth of organisms in endotracheal tube secretions; or necrotising enterocolitis with pnmotusitis 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 ≥5 x 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 effect 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. 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, may have contributed to neutropenia.

Thrombocytopenia was a possible complication of treatment and has not been reported before. 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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