The effect of glucose-6-phosphate dehydrogenase deficiency on the severity of neonatal jaundice in Cape Town

P. ROUX, C. D. KARABUS, P. S. HARTLEY

Summary
A study was made of 3718 newborn infants with jaundice in excess of physiological levels. Prematurity, haemolytic disease, haematomas or infections were present in 1278 patients. Of the remaining 2440 neonates, 137 were deficient in glucose-6-phosphate dehydrogenase (G-6-PD) and 2303 had idiopathic hyperbilirubinaemia. Exchange transfusion was necessary in 59 (42.7%) of the patients with G-6-PD deficiency and in 426 (18.5%) of those with idiopathic hyperbilirubinaemia. Kernicterus occurred in 3 infants (2.2%) with G-6-PD deficiency and in 3 (0.13%) with idiopathic hyperbilirubinaemia. These findings indicate that G-6-PD deficiency contributes significantly to the severity of neonatal jaundice in the population group studied and should be regarded as a potentially dangerous condition.

Patients and methods
Between January 1970 and December 1978, 3718 infants were admitted to the Neonatal Jaundice Unit at the Red Cross War Memorial Children's Hospital. Of these, 3377 (91%) were of Coloured ethnic origin, 303 (8%) were Black and 38 (1%) were White. All had been given 1,000 mg vitamin K intramuscularly shortly after birth. Some of the patients were born at home and others at maternity homes or midwife obstetric units from which they were discharged soon after delivery. They were followed up by district midwives and referred to the hospital for assessment of jaundice. The infants admitted to the Neonatal Jaundice Unit were those whose serum unconjugated bilirubin levels exceeded the concentrations shown in Fig. 1. Patients with physiological jaundice were thus excluded. No infants who were obviously infected or had respiratory distress were admitted to the unit. Phototherapy was given to all the infants. Full-term infants received an exchange transfusion when the serum unconjugated bilirubin level exceeded 350 μmol/l. The infants were followed up at an outpatient clinic for a minimum of 3 months, and for at least 1 year if they had had an exchange transfusion. General and neurological examinations and a full blood count were performed at each visit.

There are differences of opinion as to the aetiological significance of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency in neonatal jaundice. Studies in Taiwan, Greece, Sardinia, Malaya and Nigeria have shown an association between G-6-PD deficiency and severe jaundice in newborn infants with a consequent increase in frequency of both exchange transfusion and kernicterus. However, no such relationship could be demonstrated in American Negro infants born at term and the enzyme deficiency was not found to be an important cause of severe jaundice in Thai or Israeli babies.

The present study was carried out to examine an impression that G-6-PD-deficient neonates in Cape Town have a more severe degree of jaundice and require exchange transfusions more frequently than do infants with idiopathic hyperbilirubinaemia.

Routine investigations included a full blood count performed on a Coulter Model S electronic counter, a reticulocyte count, blood grouping, a direct antiglobulin test using a broad-spectrum reagent and measurements of the total and conjugated serum bilirubin concentrations. Urine was examined for evidence of infection and for reducing sugars. The brilliant cresyl blue decolorization test of Morulsky et al. was used as a screening test for G-6-PD deficiency. Patients with a significantly prolonged result (> 90 minutes) on two separate occasions were considered to be G-6-PD-deficient. Erythrocyte G-6-PD was assayed quantitatively by the method of Zinkham et al. in 32 infants found to be deficient by the screening test. There was good agreement between the tests and in only 1 instance (3%) did the screening test give a false-positive result. Other
investigations such as agglutination tests for congenital infections, thyroid function tests and hepatic enzyme assays were carried out when indicated. Blood grouping, tests for syphilis and screening for Rh and other blood group antibodies were performed on all mothers.

**Results**

Of the 3718 infants, 1278 were born preterm or were found to have iso-immune haemolytic disease of the newborn, congenital haemolytic anaemia, infections or cephalohæmatoma or other confined haemorrhage. These babies were excluded from the study. There remained 2440 full-term jaundiced infants of whom 137 had G-6-PD deficiency and 2303 had idiopathic hyperbilirubinaemia. Coloured infants accounted for 96% of the G-6-PD-deficient group. The serum unconjugated bilirubin concentration exceeded 350 µmol/l (necessitating exchange transfusion) in 59 (42.7%) of the 137 babies with G-6-PD deficiency and in 426 (18.5%) of the 2303 infants with idiopathic hyperbilirubinaemia (Table I). The difference is statistically significant ($P < 0.005$).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. requiring exchange transfusion</th>
<th>No. exchange transfusion</th>
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<tbody>
<tr>
<td>G-6-PD deficiency</td>
<td>137</td>
<td>59 (42.7%)</td>
</tr>
<tr>
<td>Idiopathic hyperbilirubinaemia</td>
<td>2303</td>
<td>426 (18.5%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2440</td>
<td>485 (19.9%)</td>
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Kernicterus was noted in 6 of the infants (Table II). This complication occurred in 3 (2.2%) of the 137 G-6-PD-deficient neonates and in 3 (0.13%) of the 2303 infants with idiopathic hyperbilirubinaemia ($P < 0.05$).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Kernicterus infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-6-PD deficiency</td>
<td>137</td>
</tr>
<tr>
<td>Idiopathic hyperbilirubinaemia</td>
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<td><strong>Total</strong></td>
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Ten patients with G-6-PD deficiency were anaemic (haemoglobin concentration below 13.5 g/dl) and a further 10 had reticulocyte counts greater than 6%. In 1 case, both anaemia and reticulocytosis were present. In the remaining 116 infants with G-6-PD deficiency (84.7%) both the haemoglobin concentration and the reticulocyte count were within normal limits.

**Discussion**

This study confirms the impression that infants with G-6-PD deficiency in Cape Town born at term have a disproportionately high incidence of severe hyperbilirubinaemia and kernicterus. Fifty-nine of the 137 infants (43%) required exchange transfusion. This indicates that the G-6-PD-deficient newborn is at significantly greater risk of developing extreme jaundice than the infant with idiopathic hyperbilirubinaemia, born at term, in whom the exchange transfusion rate was only 19%. The factors responsible for the greater severity of jaundice in G-6-PD-deficient infants are not entirely clear, but at least four precipitating causes may be considered: (i) haemolysis due to the enzyme deficiency; (ii) exogenous haemolytic agents; (iii) endogenous factors such as ascorbic acid, hypoxia or altered levels of ascorbic acid and vitamin E; and (iv) ethnic group predisposition.

In the great majority (85%) of the infants, overt haemolysis was not present, as shown by a normal haemoglobin concentration and reticulocyte count. This is similar to the findings in other studies. Patients with G-6-PD deficiency alone may, however, have a slight shortening of their red cell life span. A small increase in the rate of red cell destruction, insufficient to produce anaemia, cannot be excluded as the cause of more severe jaundice in a neonate whose liver has not yet achieved its maximal ability to conjugate bilirubin. None of the infants had a history of exposure to vitamin K analogues with oxidant properties or to any other potential chemical cause of haemolysis and these agents cannot therefore be incriminated as contributing to the hyperbilirubinaemia. Preterm infants were excluded from this study and endogenous factors such as acidosis and hypoxia were not present in the infants described here who, apart from the 6 with kernicterus, were all vigorous, healthy babies born at term. The low concentration of vitamin E in the serum of the newborn infant and its consequent reduced anti-oxidant effect may, in the presence of reduced G-6-PD activity, make it difficult for the red cell to metabolise the excess $\text{H}_2\text{O}_2$ constantly being formed within it. Similarly the elevated vitamin C level often present in the newborn stimulates the erythrocyte pentose phosphate metabolic pathway. Together with G-6-PD deficiency this may exhaust the red cell’s ability to maintain enough reduced glutathione and so produce haemolysis.

The lack of signs of haemolysis in G-6-PD-deficient infants has led to the investigation of another mechanism for severe neonatal jaundice. Meloni et al. have shown that the liver of the newborn with G-6-PD deficiency is less able to form glucuronide conjugates than the liver of a normal infant. They feel that reduced hepatic bilirubin conjugation rather than excessive haemolysis may be responsible for the more severe jaundice in the G-6-PD-deficient infant. This view was supported by the finding that barbituric acid was effective in lowering serum bilirubin concentration in G-6-PD-deficient newborns.

Finally, in view of the conflicting reports from different countries, it may be that an ethnic predisposition towards neonatal hyperbilirubinaemia, in addition to the G-6-PD deficiency, is a necessary factor in the aetiology of severe neonatal jaundice. Of the infants reported here almost all were Coloured. Newborn infants of this population group who have G-6-PD deficiency are therefore at risk of developing severe hyperbilirubinaemia.

In our experience G-6-PD deficiency is a potentially serious condition in the newborn infant and these patients should be carefully observed. Signs of haemolysis are rarely present and the infants are clinically indistinguishable from those with idiopathic hyperbilirubinaemia. Tests for G-6-PD deficiency should be performed in cases of severe and otherwise unexplained neonatal jaundice before a diagnosis of idiopathic hyperbilirubinaemia is made.

**REFERENCES**