Plasma 25-hydroxyvitamin D and rickets in infants of extremely low birthweight

N MCINTOSH, A LIVESEY, AND O G BROOKE

Department of Child Health, St George's Hospital Medical School, London

SUMMARY  Rickets is now a well-known entity in infants of very low birthweight. In a 1-year period (1981) 8 of 15 neonatal survivors whose birthweight was less than 1000 g (extremely low birthweight) developed rickets despite high supplementation with ergocalciferol, 2000 units a day. At the time of radiological diagnosis their postnatal age was 8 (range 5–14) weeks, and they all had normal or high plasma concentrations of 25-hydroxyvitamin D (mean 80 nmol/l, range 40–160 nmol/l). Although 4 infants received alfacalcidol which healed the rickets, in 4 infants the rickets healed spontaneously without change in treatment. The results suggest that inadequate vitamin D supplementation is not the cause of rickets in such infants.

The incidence of rickets in infants of low birthweight may be as high as 32%.1,2 Spontaneous rib fractures3 and late onset respiratory distress4 may lead to significant morbidity in this fragile group of babies. The aetiology of the condition is unclear. Although calcium5 and phosphorus substrate deficiency6 have both been postulated, many people consider that inadequate vitamin D intake7 or metabolism is more likely to be the cause. Hillman and Haddad8 found inadequate 25-hydroxylation of vitamin D in the liver of the preterm baby but Wolf et al.9 found that 25-hydroxylation was possible after 32–34 weeks’ gestation. Scino et al.10 postulated a problem of 1-α-hydroxylation in the kidney and Glasgow and Reid11 were able to heal the rickets with alfacalcidol. The aim of our study was to determine the incidence of rickets in babies less than 1000 g nursed in our unit and to establish whether insufficient vitamin D intake was the cause.

Patients and methods

During 1981, 29 babies weighing less than 1000 g at birth were admitted to the neonatal unit at St George’s Hospital. Two infants, born on site, had lethal malformations and were not offered intensive care. Of the 27 remaining infants 15 (56%) survived for at least 28 days, only 1 of these subsequently dying after surgery for intussusception at age 9 weeks.

Eight (53%) cases of rickets occurred in the 15 neonatal survivors. The median weight was 840 (range 700–990) g and median gestation 27·5 (range 25–28) weeks. All infants were appropriate weight for gestation, and the racial origin was similar to general admissions to the neonatal unit (5 white, 1 African, 1 Indian, 1 West Indian). The diagnosis of rickets was established radiologically by an independent radiologist at a mean age of 8 (range 5–14) postnatal weeks on the basis of cupping and fraying of the epiphyses with splaying of the ends of the shaft of the radius.

All infants developing rickets had received 2000 units of vitamin D daily from age 7 days (1600 units of ergocalciferol and 400 units in a multivitamin preparation). All infants were initially fed on expressed breast milk, either fresh from the mother or, if from a donor, generally pasteurised. Five infants received only expressed breast milk. One 3-week-old infant was changed to Prematalac because of hypoproteinaemic oedema and 2 others were changed to Prosopee at age 8 weeks (rickets was evident before this change was made). The maximum volume of milk was 220 ml/kg a day. No supplementary calcium or phosphorus was given.

The clinical problems of these babies are shown in Table 1. Levels of plasma calcium, phosphorus, and alkaline phosphatase were measured regularly, about fortnightly, and wrist x-ray films were performed if the alkaline phosphatase levels were greatly raised.

Plasma calcium,12 phosphorus,13 and alkaline phosphatase14 were measured using our standard laboratory autoanalyser methods (Technicon AA II). When rickets was diagnosed, plasma 25-hydroxyvitamin D was measured by competitive protein-binding assay.15

At the time of diagnosis 4 infants were moderately
Table 1  Rickets in 8 infants of extremely low birthweight

<table>
<thead>
<tr>
<th>Clinical conditions</th>
<th>Number of infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>5</td>
</tr>
<tr>
<td>Ventilation (more than 7 days)</td>
<td>5</td>
</tr>
<tr>
<td>Intravenous feeding (more than 7 days)</td>
<td>5</td>
</tr>
<tr>
<td>Regular treatment with frusemide</td>
<td>4</td>
</tr>
<tr>
<td>Regular treatment with bicarbonate</td>
<td>3</td>
</tr>
<tr>
<td>Chest infection</td>
<td>3</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>3</td>
</tr>
<tr>
<td>Subglottic stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Jaundice of intravenous feeding</td>
<td>1</td>
</tr>
<tr>
<td>Gut problems (intussusception)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2  Biochemical findings at diagnosis of rickets in 8 infants of extremely low birthweight

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.32</td>
<td>2.05-2.57</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.13</td>
<td>0.4-1.7</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>919</td>
<td>552-1215</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (nmol/l)</td>
<td>80</td>
<td>40-160</td>
</tr>
</tbody>
</table>

Conversion: SI to traditional units—calcium: 1 mmol/l=4 mg/100 ml; phosphate: 1 mmol/l=3.09 mg/100 ml; 25 hydroxyvitamin D: 1 nmol/l=0.04 ng/ml.

ill with respiratory problems and although these were not considered to be primarily of rachitic origin it was thought prudent to change their vitamin D therapy to 0.33 μg alfalcacidol daily. The remaining 4 infants were observed without change in vitamin D therapy.

Results

The plasma concentrations of calcium, phosphorus, and 25-hydroxyvitamin D, and the activity of plasma alkaline phosphatase are shown in Table 2. Although the mean plasma calcium and phosphorus levels were in the normal range, 2 patients were hypocalcaemic and 1 hypophosphataemic compared with our normal paediatric range. The alkaline phosphatase activity ranged between 552 and 1215 U/l. Only one patient had isoenzyme fractionation which confirmed a predominantly bone pattern. The plasma 25-hydroxyvitamin D levels were either well within the normal range for our laboratory (20–150 nmol/l) or high. The use of 1 alfalcacidol was associated with radiological improvement over about 3 weeks' treatment, but the infants who had no change in treatment also showed radiological improvement.

Discussion

The incidence of rickets in this group of extremely low birthweight infants is higher than has so far been reported. There were not considered to be primarily of rachitic origin it was thought prudent to change their vitamin D therapy to 0.33 μg alfalcacidol daily. The remaining 4 infants were observed without change in vitamin D therapy.

Results

The plasma concentrations of calcium, phosphorus, and 25-hydroxyvitamin D, and the activity of plasma alkaline phosphatase are shown in Table 2. Although the mean plasma calcium and phosphorus levels were in the normal range, 2 patients were hypocalcaemic and 1 hypophosphataemic compared with our normal paediatric range. The alkaline phosphatase activity ranged between 552 and 1215 U/l. Only one patient had isoenzyme fractionation which confirmed a predominantly bone pattern. The plasma 25-hydroxyvitamin D levels were either well within the normal range for our laboratory (20–150 nmol/l) or high. The use of 1 alfalcacidol was associated with radiological improvement over about 3 weeks' treatment, but the infants who had no change in treatment also showed radiological improvement.

Discussion

The incidence of rickets in this group of extremely low birthweight infants is higher than has so far been reported. These infants generally had had compli-
We thank Dr I Brown for measurements of plasma 25-hydroxyvitamin D, Mrs S Garrett for secretarial help, and medical and nursing staff on the neonatal unit for clinical management of the babies.

References

12 Technicon. Method AA II 03.

Correspondence to Dr N McIntosh, Department of Child Health, St George’s Hospital Medical School, Cranmer Terrace, London SW17 0RE.

Received 2 July 1982