Recommendations for the management of galactosaemia

J H Walter, J E Collins, J V Leonard, on behalf of the UK Galactosaemia Steering Group

There is controversy about certain aspects involving the detection, outcome, and management of galactosaemia. The relative rarity of the disorder and lack of prospective studies have made it difficult for paediatricians to base their advice to parents and their management of patients on good clinical evidence. The UK Galactosaemia Steering Group was established in 1994 to address these problems. It is now maintained by the research division of the Royal College of Paediatrics and Child Health. The primary aim of this steering group is to set up a national register of all cases of galactosaemia and to obtain detailed prospective longitudinal data.

Having established this register it has become apparent that the management of galactosaemia varies widely. Patients are seen in many centres within the UK, both specialist and non-specialist. We believe it would be helpful for clinicians involved in their care to have recommendations for management based on currently available information. The recommendations represent a consensus view of the steering group. Those for the treatment of hypergonadotrophic hypogonadism in galactosaemia have been agreed with the British Society for Paediatric Endocrinology and Diabetes.

**Classical galactosaemia**

Classical galactosaemia is caused by an inherited deficiency of the enzyme galactose-1-phosphate uridyl transferase. Incidence in the UK is approximately 1:45,000 live births; most patients are either homozygous or heterozygous for the Q188R mutation. Classical galactosaemia most often presents in the neonatal period with life threatening illness. Excluding galactose from the diet combined with supportive care is essential to treat this acute illness and prevent further deterioration. Galactose restriction throughout life is necessary to stop recurrence of severe toxicity. However, early diagnosis and appropriate dietary treatment does not prevent long term complications including cognitive dysfunction, which may worsen with age, and gonadal dysfunction in female patients. Recent evidence suggests that there is endogenous production of galactose and this may be responsible for these long term effects. Follow up throughout life is necessary.

**Diagnosis**

Early diagnosis is essential. Neonatal screening is not routine in England and Wales. Even with screening the results of the assay are likely to be available only after the onset of clinical illness. Most infants present in the first weeks of life. Rarely patients may present after the newborn period.

**Most common symptoms and signs**

- Poor feeding and poor weight gain
- Vomiting and diarrhoea
- Jaundice
- Cataracts
- Lethargy and hypotonia
- Hepatomegaly
- Encephalopathy
- Full fontanelle
- Bleeding or excessive bruising
- Improvement on intravenous fluids.

**Abnormal findings**

**Liver dysfunction**

- Unconjugated or combined hyperbilirubinaemia
- Abnormal liver function tests
- Abnormal clotting
- Raised plasma amino acids (particularly phenylalanine, tyrosine and methionine)
- Raised phenylalanine may result in a false positive neonatal screening test for phenylketonuria.

**Renal tubular dysfunction**

- Metabolic acidosis
- Galactosaemia (after feeds containing galactose or lactose) and glycosuria
- Albuminuria
- Aminoaciduria.

**Abnormal carbohydrate metabolism**

- Increased plasma galactose
- Increased red blood cell galactose-1-phosphate
- Increased urine and blood galactitol

**Haemolytic anaemia**

*Escherichia coli*

**Diagnostic investigations**

Beutler test—A fluorescent spot test for galactose-1-phosphate uridyl transferase activity, now widely used for the diagnosis of galactosaemia. False negative results may occur following recent blood transfusions (within three
months) and false positive results with glucose-6-phosphate dehydrogenase deficiency.

**Red blood cell galactose-1-phosphate uridylic transferase assay**—A quantitative assay to confirm the diagnosis. It also identifies variants with residual enzyme activity. False negative results may occur within three months of a blood transfusion. If there are problems establishing a diagnosis, galactose-1-phosphate uridylic transferase can be measured in red cells from both parents to establish their carrier state.

**Red blood cell galactose-1-phosphate**—Galactose-1-phosphate concentrations are always raised in classic galactosaemia and are not significantly affected by blood transfusions.

**DNA analysis**—Approximately 60% of UK patients with classic galactosaemia are homozygous for the Q188R mutation. The presence of reducing substances or galactose in urine is neither sensitive nor specific. Small quantities of galactose are commonly found in the urine of any patient with liver disease and a non-specific glycosuria can occur with galactosaemia caused by tubular damage. Galactose may also disappear rapidly from the urine in patients with galactosaemia.

**Prenatal diagnosis**—Galactose-1-phosphate uridylic transferase assay in cultured amniotic fluid cells or in chorionic villus biopsies, by galactitol estimation in amniotic fluid supernatant, or by mutation analysis of DNA extracted from chorionic villus biopsy if the genotype of the index case has been characterised.

**Initial management**

If there is any suspicion of the diagnosis (either biochemical or clinical) galactose must be excluded from the diet (table 1 lists galactose free formulae).

Supportive care should be provided as required, dependent on the severity of liver, renal, and central nervous system disease. Antibiotics, intravenous fluids, plasma, and vitamin K are often necessary. Continue a galactose free formula after confirming the diagnosis. Refer to regional centre for specialist paediatric, dietetic, and biochemical support.

**Table 1 Milk substitutes suitable for infants with galactosaemia (and prescribable in the UK on FP10 designated ACBS)**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Manufacturer</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infasoy</td>
<td>Cow &amp; Gate</td>
<td>Lactose free soya preparation</td>
</tr>
<tr>
<td>Wysoy</td>
<td>SMA Nutrition</td>
<td>Lactose free soya preparation</td>
</tr>
<tr>
<td>Prosobee</td>
<td>Mead Johnson</td>
<td>Lactose free soya preparation</td>
</tr>
<tr>
<td>Farleys Soya Formula</td>
<td>Farley Group</td>
<td>Lactose free soya preparation</td>
</tr>
<tr>
<td>Isomil</td>
<td>Ross Products Division</td>
<td>Lactose free soya preparation</td>
</tr>
<tr>
<td>MCT Peptide 0-2</td>
<td>SBS</td>
<td>For infants with severe liver disease</td>
</tr>
<tr>
<td>Prevestimil</td>
<td>Mead Johnson</td>
<td>MCT containing preparation, lactose free</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For infants with severe liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCT containing preparation. Contains up to 0.8 mg lactose/100 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contains up to 3 mg lactose/100ml, therefore not recommended as first choice</td>
</tr>
<tr>
<td>Enfamil S3</td>
<td>Mead Johnson</td>
<td>Calcium—500 Renacare</td>
</tr>
<tr>
<td>AL 110</td>
<td>Nestlé</td>
<td>Calcium lactate 300 mg tabs</td>
</tr>
<tr>
<td>Galactamin 17</td>
<td>Cow &amp; Gate</td>
<td>Calcium lactate 300 mg tabs</td>
</tr>
</tbody>
</table>

**Biochemical findings**

**RED CELL GALACTOSE-1-PHOSPHATE**

Concentrations of red cell galactose-1-phosphate have been widely used to monitor dietary compliance. Concentration of this metabolite is often extremely high at diagnosis and it...
is essential to demonstrate its decline to acceptable values after introducing the diet. This usually occurs within a few weeks but, for unknown reasons, can occasionally take as long as a year. The units used to express galactose-1-phosphate concentrations vary between different laboratories. Target concentrations differ, to some extent, according to methodology but generally the upper limit of the acceptable range quoted in different units are as follows:

- µmol/l red cells, 150
- µg/ml packed cells, 50
- mg/100 ml, 5
- µmol/g haemoglobin, 0.5

In patients with classic galactosaemia, despite dietary adherence, galactose-1-phosphate concentrations never decline to those found in healthy individuals (close to 0).

Long term monitoring of classic galactosaemia by frequent measurements of red cell galactose-1-phosphate is unjustified. The laboratory costs are high; a given value reflects only galactose intake in the previous 24 hours; and no correlation with long term clinical outcome has been shown. Raised concentrations may indicate continuous and serious deviations from the diet but some patients have unusually high values despite meticulous dietary compliance. Galactose-1-phosphate concentrations do not vary greatly in individual patients providing dietary compliance is reasonable. A suggested scheme for the frequency of monitoring galactose-1-phosphate levels is as follows:

- < 1 year, every three months
- 1–14 years, every six months
- > 14 years, annually

**Urinary galactitol**

Urinary galactitol has been investigated as a means of monitoring diet but, although it may appear to have some practical and theoretical advantages compared with galactose-1-phosphate, its value remains to be validated. It may prove useful in patients in whom cataracts fail to resolve or recur. The assay is only available in a few centres.

**Development**

Neurodevelopmental problems are common in children with galactosaemia. In preschool years speech problems are frequent and severe. Development may be generally delayed but it is more common for cognitive problems to become apparent during school years. Regular assessment of development and cognitive function are indicated using standardised tests—for example, Griffiths scales, Bailey scales, British ability scales. In particular, assessment should be directed towards early detection of speech impairment. Many children require speech therapy and additional help at school. Ataxia and intention tremor may occur in older children and adults.

**Ophthalmological findings**

Slit lamp examination for cataract assessment should be made at the time of diagnosis, every six months until 3 years of age, and then annually.

**Growth**

Growth in infancy and childhood should be normal providing the diet is adequately supervised.

**Osteoporosis**

A satisfactory calcium intake should be maintained to protect patients from osteoporosis. Some units advocate regular assessments of bone density.

**Pubertal development in girls with galactosaemia**

Hypergonadotrophic hypogonadism occurs in most girls over 14 years of age with galactosaemia. Most women are infertile. Pubertal development and fertility are normal in boys.

**Endocrine investigations and treatment in girls**

Follicle stimulating hormone, luteinising hormone, and oestradiol should be measured at 6 months and then at 10 and 12 years old (and if necessary yearly thereafter). Referral to a paediatric endocrinologist should be made by the time the patient is 10 years old.

We recommend hormone treatment from 12 years of age (some recommend 13 years if the girl is short) with raised basal gonadotrophin concentrations and low oestradiol. One recommended regimen is as follows:

- Ethinyl oestradiol 2 µg daily for the first year—if pubertal advance is particularly slow then the time on this dose should be reduced to six months
- Ethinyl oestradiol 5 µg daily for the second year
- Ethinyl oestradiol 10 µg daily for the third year—the patient and parents should be informed that vaginal spotting or withdrawal bleeds may occur during this year; if this is the case, a progestogen should be added at the start of each month
- Loestrin (an oral contraceptive preparation containing 20 µg ethinyl oestradiol and a progestogen) given in the usual way (daily for 21 days followed by 7 days abstinence). This preparation should be adequate for most young women. If there is breakthrough bleeding or any other symptoms of oestrogen deficiency then a preparation containing 30 µg of ethinyl oestradiol can be used. (Natural oestrogens would be an acceptable alternative to synthetic oestrogens.)

NB—All tablet preparations contain small quantities of lactose but the total dose is very small compared with endogenous production.

Outpatient review should be every four months during the first two years of hormone treatment and every six months thereafter. The following should be monitored:

- physical development and growth throughout these years of pubertal induction
- bone age yearly from the start of treatment
- pelvic ultrasound (for uterine dimensions) at the start of treatment and after two and four years
- blood pressure.
Special care and advice should be given to patients with a family history or past history of venous thrombosis and to those who are overweight or smoke.

Conclusions
These recommendations are based on our current understanding of galactosaemia. It is evident that there is still much to learn about this disorder. We would welcome comments from others involved in the care of children and adults with galactosaemia. As more data become available from the galactosaemia register and elsewhere, these recommendations will be updated.


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We publish this paper because we realise that many patients with galactosaemia are cared for outside specialist units and it will benefit children and their doctors to have the views of the steering group.

They are recommendations—not rules—and we remind readers that our general policy when deciding whether to accept for publication guidelines and consensus statements remains the same.

M CHISWICK
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