Urinary oxalate and glycolyce excretion and plasma oxalate concentration

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Abstract
The diagnosis of primary hyperoxaluria in young children is hampered by the lack of a reliable reference range for urinary oxalate excretion, especially in infants. We present data on urinary oxalate and glycolytic excretion in 137 normal children, on the plasma oxalate concentration in 33 normal children and 53 with chronic renal failure, and on amniotic fluid oxalate concentration in 63 uncomplicated pregnancies. The urinary oxalate:creatinine molar ratios were log normally distributed: mean (range) values were <1 year 0·061 (0·015–0·26), 1–5 years 0·036 (0·011–0·12), 5–12 years 0·030 (0·005–0·15), and >12 years 0·013 (0·002–0·083). Geometric mean (range) plasma oxalate concentration in the normal children was 1·53 (0·78–3·02) µmol/l and was independent of age. The mean (SD) plasma oxalate:creatinine molar ratio in these normal children and 50 with chronic renal failure was 0·033 (0·013), and was independent of age and renal function. Mean (SD) amniotic fluid oxalate concentration was 19·0 (4·3) µmol/l.

Primary hyperoxaluria type I is an inborn error of glycolate metabolism characterised by excessive production and urinary excretion of oxalate and glycolate.1 Two thirds of the cases present before the age of 5 years with calcium oxalate urolithiasis, and the disease usually runs a progressive course leading to end stage renal failure with systemic oxalosis before adulthood. It is important to diagnose the condition at an early stage so that therapeutic measures can be implemented to reduce the severity of the disease by modifying the risk factors associated with the deposition of calcium oxalate in the urinary tract and in the tissues.

There is, however, a paucity of information in the literature on the urinary excretion rates and plasma concentrations of oxalate and glycolate in young normal children. The report by Gibbs and Watts gives values for urinary oxalate excretion in a few normal children, the youngest of whom was 2·5 years of age,2 and the preliminary report of Kasidas and Rose presented only limited data on children under 1 year of age.3 Without reliable reference ranges the interpretation of urinary oxalate concentrations in young children has been uncertain. There is also some doubt about the appropriate correction of oxalate excretion for body size, and in any case the collection of accurately timed urine specimens from young children is notoriously difficult. In some cases a urine sample is unobtainable because of anuric renal failure: in these circumstances the association between the plasma concentrations of oxalate and creatinine has been used to support the diagnosis of primary hyperoxaluria, but again reference ranges are lacking. Finally, we considered the possibility of prenatal diagnosis of the disorder from amniotic fluid oxalate concentration, but good normal data were not available.

To address these problems we measured: (i) urinary oxalate:creatinine and (ii) glycolate: creatinine molar ratios in 137 'normal' children; (iii) plasma oxalate and creatinine concentrations in 33 'normal' children and 53 children with renal damage; and (iv) amniotic fluid oxalate concentration from 63 uncomplicated pregnancies.

Patients and methods
The group of 137 'normal' children were aged 0·1 to 17·0 years, and consisted of patients admitted to the Hospital for Sick Children, Great Ormond Street, London, for minor surgery unrelated to the urinary or gastrointestinal tract, their siblings, and the children of the staff and their friends. The height and weight were known in 92 of them. The urine sample obtained was the second in the morning—that is, the first sample passed after the overnight urine had been voided. Plasma was obtained from 33 of the children admitted for minor surgery who were having blood taken for clinical purposes and from 53 children attending the renal clinic of the hospital with various degrees of renal failure. Samples of amniotic fluid were obtained from 63 pregnant women at 16–18 weeks’ gestation undergoing amniocentesis at St George’s Hospital, London.

Oxalate concentration was measured enzymatically with immobilised oxalate oxidase,3,4 glycolate concentration with glycolate oxidase,5 and creatinine by Autoanalyser II using a modified Jaffé alkaline picrate reaction. For plasma and amniotic fluids, ultrafiltrates were prepared for analysis using Amicon Centriflo ultrafiltration membrane cones with molecular weight cut off of 25 000 daltons.

Some of the data were log normally distributed: means, ranges, and correlations were therefore calculated on log transformed results. Surface area was calculated from the formula of Dubois and Dubois.6

Results
(i) URINE OXALATE:CREATININE MOLAR RATIO
The urine oxalate:creatinine molar ratio (UOx:
UCr) decreased with age \((r=-0.50, p<0.0001)\) (fig 1). The regression equation was:

\[
\log (\text{UOx:UCr}) = -1.27 - 0.0425 \times \text{age (years)}
\]

Mean and ranges calculated on log transformed data are given in the table. UOx:UCr was significantly higher in infants than in older children \((p<0.001)\). In the 92 children for whom height and weight were known, log (UOx:UCr) correlated similarly with age \((r=-0.50)\), weight \((r=-0.50)\), and surface area \((r=-0.48)\), better than with height \((r=-0.40)\), but the correlation coefficients were not significantly different from each other.

(ii) Urine Glycolate:Creatinine Molar Ratio

The urine glycolate:creatinine ratio (Ugly:UCr) also declined with age \((r=-0.32, p<0.0005)\) (fig 2):

\[
\log (\text{UGly:UCr}) = -1.60 - 0.0223 \times \text{age (years)}
\]

The decline in Ugly:UCr with age was less than that of UOx:UCr, and as a consequence, UOx:UGly also declined with age \((r=-0.27, p<0.005)\) (fig 3):

\[
\log (\text{UOx:UGly}) = -0.323 - 0.0200 \times \text{age (years)}
\]

(iii) Plasma Oxalate and Creatinine Concentrations

In the healthy children the plasma oxalate (POx) concentration was independent of age \((r=0.09, p>0.1)\) or plasma creatinine concentration (PCr). Geometric mean (range) POx was 1.53 (0.78–3.02) mmol/l. When the children with renal disease were included there was a highly significant correlation between POx and PCr, which were both log normally distributed \((r=0.93, p<0.0001)\) (fig 4). The regression equation was:

\[
\log \text{POx} = -1.39 + 0.94 \times \log \text{PCr}
\]

This association gives POx=1.6 mmol/l when PCr=50 mmol/l, and POx=14.4 mmol/l when PCr=500 mmol/l. The mean (SD) POx:PCr ratio was 0.033 (0.013), was independent of age, and never exceeded 0.07.

(iv) Amniotic Fluid Oxalate Concentration

Amniotic fluid oxalate concentration was approximately normally distributed with a mean (SD) of 19.0 (4.3) mmol/l.

<table>
<thead>
<tr>
<th>Urinary oxalate and glycolate excretion</th>
<th>&lt;1 year ((n=27))</th>
<th>1–&lt;5 years ((n=67))</th>
<th>5–&lt;12 years ((n=31))</th>
<th>&gt;12 years ((n=12))</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOx:UCr (mmol:mmol)</td>
<td>0.061 (0.015–0.26)</td>
<td>0.036 (0.011–0.12)</td>
<td>0.030 (0.005–0.15)</td>
<td>0.013 (0.002–0.083)</td>
</tr>
<tr>
<td>Ugly:UCr (mmol:mmol)</td>
<td>0.024 (0.007–0.070)</td>
<td>0.023 (0.005–0.091)</td>
<td>0.016 (0.005–0.046)</td>
<td>0.013 (0.006–0.041)</td>
</tr>
<tr>
<td>UOx:UGly (mmol:mmol)</td>
<td>2.6 (0.49–0.7)</td>
<td>1.6 (0.50–4.9)</td>
<td>1.0 (0.41–8.1)</td>
<td>1.0 (0.21–5.1)</td>
</tr>
</tbody>
</table>

Mean (range) calculated on logged data.
Urinary and glycolate steeply rather than values in young slightly lower the hyperoxaluria. However, Leumann et al reported another case where primary hyperoxaluria was subsequently confirmed despite a normal level of oxalate in the amniotic fluid. With the elucidation of the primary enzyme defect, antenatal diagnosis by fetal liver biopsy has now become possible for type 1 primary hyperoxaluria. However, this is a highly specialised procedure not always available and does not detect type 2 hyperoxaluria. Hence there may still be a role for the measurement of amniotic fluid oxalate concentration, which needs to be further evaluated.

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