Sapropterin testing in a paediatric centre – the Queensland experience of testing children under 18 years old for a tetrahydrobiopterin responsive form of phenylketonuria

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Introduction
Phenylketonuria (PKU) is an autosomal recessive disorder of phenylalanine (PHE) metabolism due to a deficiency in phenylalanine hydroxylase for which tetrahydrobiopterin (BH4) is the cofactor. In 2019, the Australian government approved funding of sapropterin dihydrochloride, an oral synthetic form of BH4, in children with PKU who demonstrated a ≥30% reduction in PHE to a sapropterin load test. This retrospective project details results of Queensland’s first twelve months following approval of sapropterin.

Method
9 infants and 89 children qualified to either a 24-hour (infants) or 7-day (children) sapropterin load test using a dose of 20mg/kg, with all 9 infants and 69 children participating.

Test Design and Procedure
Prior to commencement of the 7-day load test, a comprehensive 3-day diet history was completed by the family and reviewed by the metabolic dietitian as well as weekly blood samples in the four weeks prior to starting. Day 1 of testing, dried blood spot cards were collected to measure PHE and Tyrosine (Tyr) at baseline +2 hours, +4 hours, + 8 hours and + 24 hours post the initial dose of sapropterin.
For newborns the BH4 load test was complete after the final blood sample at 24 hours post the initial dose of sapropterin.
Days 2 – 7 of testing, children were instructed to collect a DBS card on waking, take the dose of sapropterin and then continue their prescribed protein allowance and PKU formula as determined by the metabolic dietitian.
Results

<table>
<thead>
<tr>
<th></th>
<th>PKU patients</th>
<th>Total tested</th>
<th>Responsive</th>
<th>Non-responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU &gt;30 days</td>
<td>89</td>
<td>69</td>
<td>44 (71%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Infants diagnosed on NBS</td>
<td>9</td>
<td>9</td>
<td>4 (44%)</td>
<td>5 (56%)</td>
</tr>
</tbody>
</table>

Days taken for children to respond

Discussion
✓ Metabolic dietitians managed dietary challenges pre and post testing
✓ Those with a result greater than 60% responsiveness showed the most clinical benefit
✓ For those with responsiveness less than 50%, it can take up to 6 months to determine clinical responsiveness
✓ An unexpected result was the number (40%) of patients who responded between days 2 – 6.
✓ Dietary adjustment has been implemented during illness to maintain adequate phenylalanine control during episodes of catabolism.

Conclusion
24% of the classical PKU (PHE >1200umol/L) population and 100% of those with a mild PKU (PHE 600-1200umol/L) responded.

Of the 44 patients who were proven responsive, results showed 26 (60%) children responded to sapropterin testing in the first 24 hours with 18 (40%) children responsive between day 2 and 6 of testing. Non-responsive infants will be offered a 7 day load test at approximately 4 years of age, when diet has been established.