CHOLINESTERASE GENOTYPING

GENOTYPING ASSAY

The routine screen consists of testing for butyrylcholinesterase (BCHE) activity and the following BCHE gene variations:

Common and Human Genome Variation Society (HGVS) Nomenclature:

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Coding DNA Change</th>
<th>Predicted Amino Acid Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibucaine</td>
<td>c.293A&gt;G</td>
<td>p.Asp98Gly</td>
</tr>
<tr>
<td>Silent-1</td>
<td>c.435delTinsAG</td>
<td>p.Phe146delinsValfs*12</td>
</tr>
<tr>
<td>K-variant</td>
<td>c.1699G&gt;A</td>
<td>p.Ala567Thr</td>
</tr>
</tbody>
</table>

Testing for Fluoride variations or rare variants by additional gene sequencing of the coding region may be performed if indicated. Testing of Dibucaine Number and Fluoride Number are no longer performed.

SPECIMEN & REQUEST

0.5 mL serum/heparinised plasma for BCHE activity (preferably collected prior to administration of anaesthetic or a minimum of 48 hours after) plus 5.0 mL EDTA whole blood for variation detection.

It is important to supply clinical details, medication and, for family studies, details of the relationship to the proband.

Transport and store refrigerated. Do not freeze. Please contact the laboratory for an estimate of turnaround times.

PRICE

The cost of measurement of BCHE activity is covered by the Medicare Schedule. The cost of detection of BCHE gene variations is not covered by the Medicare Schedule - the full cost may have to be paid by the patient.

The charge for testing the three variations in the routine screen is $100.00. Any extra investigations of the BCHE gene sequence to identify rarer variations will incur an additional charge of $100.00.

CLINICAL SIGNIFICANCE

There are two clinically important and related enzymes with the ability to hydrolyse acetylcholine:

Choline esterase I - true cholinesterase – red blood cell cholinesterase – acetylcholinesterase
Choline esterase II - pseudocholinesterase – serum cholinesterase – butyrylcholinesterase

Both enzymes are inhibited by organophosphate pesticides, the alkaloids prostigmine and physostigmine and a large variety of compounds, such as morphine, quinine, tertiary amines, phenothiazines, anti-neoplastic agents, MAO inhibitors, oral contraceptives, pyrophosphate, bile salts, citrate, fluoride and borate.

Only butyrylcholinesterase is inhibited by the muscle relaxants scoline (succinylcholine or suxamethonium) or mivacurium which may be administered during anaesthesia. Patients with persistently low BCHE activities may have deficient forms of the enzyme and an impaired ability to break down these agents. They may experience prolonged apnoea following surgery, requiring mechanical ventilation until the drugs are eliminated by other means. In a number of cases however, apnoea may entirely be due to factors other than BCHE deficiency.

The Dibucaine (syn. atypical) and Fluoride variations change the structure of the active centre of the enzyme and reduce substrate binding affinity compared to the usual form. The silent variations generally result in inactive enzyme or
enzyme with minimal catalytic activity. The K-variant variation, which is in linkage with the Dibucaine variation, may cause a further quantitative 30% reduction in BCHE activity but in the absence of the Dibucaine variation or other contributing factors, does not usually cause clinically significant BCHE deficiency or apnoea.

The incidence of the BCHE variations and their apparent effect on enzyme activity (if known) are tabulated below:

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Coding DNA variation</th>
<th>Percentage apparent reduction in enzyme activity in homozygotes</th>
<th>Percentage of carriers in Caucasian population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibucaine</td>
<td>c.293A&gt;G</td>
<td>60% (our data)</td>
<td>3.3%</td>
</tr>
<tr>
<td>Silent-1</td>
<td>c.435delTinsAG</td>
<td>&gt; 98%</td>
<td>0.22%</td>
</tr>
<tr>
<td>Fluoride-1</td>
<td>c.812C&gt;T</td>
<td></td>
<td>0.51%</td>
</tr>
<tr>
<td>Fluoride-2</td>
<td>c.1253G&gt;T</td>
<td></td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>K-variant</td>
<td>c.1699G&gt;A</td>
<td>20 - 30%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Normal BCHE activity in healthy adults has a wide range (7-14 kU/L for males and 6-14 kU/L for females). Levels in children vary with age. Newborns have levels lower than adults but by 2 months these have increased to adult values. BCHE then continues to increase above adult values through childhood, peaking by approximately 6 years of age. Thereafter, BCHE decreases and by puberty is stabilised to the adult level.

Increases in BCHE activity may be observed in patients with nephrotic syndrome, essential hypertension, asthma, psoriasis, thyrotoxicosis, haemochromatosis, alcoholism, obesity, diabetes or with anxiety and other acute psychiatric states.

In addition to pesticide poisoning, BCHE activity may be reversibly decreased in a number of clinical conditions due to decreased synthesis in the liver. Acute hepatitis, chronic hepatitis of long duration and advanced cirrhosis can cause a 30-70% decrease in activity. Decreased activity may also occur secondary to hypothyroidism, malnutrition, pregnancy, acute infections, pulmonary embolism, muscular dystrophy, carcinoma and chronic renal disease, as well as after surgery and acute myocardial infarction.

Cocaine is metabolised by BCHE. Patients with a BCHE deficiency should avoid its use.

**PATIENT FOLLOW-UP (when a variation(s) is found)**

**Homozygotes** should avoid scoline and mivacurium. Their natural siblings are advised to be tested because statistically there is a strong chance of being heterozygously or homozygously affected. Their natural parents and children would be at least heterozygously affected.

**Compound or Double Heterozygotes** should avoid scoline and mivacurium. Their natural siblings and children may be affected. At least one natural parent would be affected.

**Simple (or Single) Heterozygotes** should probably avoid scoline and mivacurium although in theory they should not manifest scoline apnoea. However, when they have clinical conditions causing low BCHE activity or undiagnosed variations affecting BCHE activity or gene expression, they may be predisposed to post-anaesthetic apnoea.

**REFERENCES**

Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 4th Ed.

Davis L et al, Anaesthesia 1997 Mar; 52(3):244-260

**ENQUIRIES**

Clinical interpretation:  A/Prof Peter Stewart (02) 9515 7162  
A/Prof David Sullivan (02) 9515 8832

Technical questions: Jennifer Burns (02) 9515 7675