The effective evaluation of thyroid status in patients on phenytoin, carbamazepine or sodium valproate attending an epilepsy clinic


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Summary: To assess the most efficient means of monitoring thyroid status in an epilepsy clinic, total thyroxine (T₄), free thyroxine (FT₄) and thyroid stimulating hormone (TSH) were measured in 71 adult patients treated long-term with either phenytoin (DPH), carbamazepine (CBZ) or sodium valproate (VAL). Twenty-seven patients with one or more abnormal thyroid hormone results were further investigated by a thyrotrophin releasing hormone (TRH) test and clinical assessment. T₄ was found to be normal in 85% on VAL, 40% on CBZ and 39% on DPH. FT₄ was normal in more patients, namely 95% on VAL, 70% on CBZ and 65% on DPH. The TRH tests indicated that FT₄ was the most efficient screening test for hypothyroidism in this epileptic population. We estimate that the use of FT₄ alone as a screening test would have reduced by 60% the number of TRH tests required.

Introduction

Long-term administration of anticonvulsant drugs is well known to affect blood thyroid hormone levels. Despite a reduction in serum total thyroxine (T₄) and free thyroxine (FT₄) most studies have emphasized that patients receiving anticonvulsants appear clinically euthyroid with normal reference levels of thyroid stimulating hormone (TSH). Nevertheless, there does seem to be a small number of patients in whom abnormalities in TSH levels do occur and cases of reversible hypothyroidism induced by phenytoin [diphenyl-hydantoin (DPH)] and carbamazepine (CBZ) have also been reported. In such patients symptoms due to the side effects of their medication may be difficult to distinguish from those due to hypothyroidism. This, therefore, means that long term monitoring of thyroid function in patients on anticonvulsants is necessary. Our objective was to study patients treated long-term with either DPH, CBZ or sodium valproate (VAL) to determine the most effective method of monitoring thyroid status in an epilepsy clinic.

Patients and methods

Seventy-one consecutive patients receiving either DPH, CBZ or VAL were studied. The patients were attending a neurology outpatient clinic and had been taking a single anticonvulsant for at least 6 months with dosage stabilized for at least 3 months prior to entry. Patients whose seizures were not controlled, or who were receiving more than one anticonvulsant drug were excluded. At the patient's clinic attendance, the serum level of DPH, CBZ or VAL was measured. In addition, thyroid function was assessed by measuring serum total thyroxine (T₄) by polyethylene glycol precipitated in-house radioimmunoassay, TSH by double antibody in-house radioimmunoassay and free thyroxine (FT₄) by a commerical kit (Coat-a-Count kit, Diagnostic Products UK Ltd). The TSH assay has a lower limit of sensitivity of 0.5 mU/L. To determine true thyroid status, patients with an abnormality of one or more of these thyroid tests were requested to attend for further investigation by a thyrotrophin releasing hormone (TRH) test, the serum TSH level being measured before, 20 and 60 minutes after an intravenous injection of 200 μg TRH (Roche). Our reference range for T₄ is 75 to 145 nmol/l, for FT₄ 10.3 to 18.9 pmol/l and for basal serum TSH is less than 4.6 mU/l. We define a normal TRH test as showing a 20 minute rise to 20 mU/l or less in a male and to
24 mU/l or less in a female with a subsequent fall at 60 minutes. A Crooks-Wayne diagnostic index for hypothyroidism was also performed.

Statistical significance was determined by the Chi-squared test for differences in distribution and the Student's t test for differences between means.

Approval for this study was given by Tayside Health Board Ethical Committee.

Results

Details of the patients, their drug dosages and prevailing serum anticonvulsant levels are shown in Table I. Those treated with CBZ or DPH had a mean basal serum T₄ and FT₄ level which was significantly lower than those treated with VAL (Table II). Significantly more patients in the VAL group had a serum T₄ and FT₄ within the normal reference range; 85% of those on VAL had a normal T₄, as compared with 40% on CBZ (P<0.001) and 39% on DPH (P<0.001). A normal FT₄ was found more often than a normal T₄; 95% of those on VAL had a normal FT₄ compared with 70% on CZB (P<0.01) and 65% on DPH (P<0.01). All the patients with a low FT₄ also had a low T₄. There was no significant difference in the distribution of normal TSH results between the 3 groups; 90% on VAL, 90% on CBZ and 94% on DPH.

In 36 patients at least one parameter was outside the reference range and on our criteria a TRH test was indicated; 27 were carried out (Table III). The reasons for not carrying out a TRH test in 9 of the patients in which it was indicated were as follows: two refused to attend, one had ceased therapy against medical advice and six had had an additional anticonvulsant drug added in the meantime to their therapy. A TRH test was indicated in these 9 patients because of a low T₄ in all of them, because of a low FT₄ in 2 and because of a basal TSH of 5.9 mU/l in one subject, although she had a normal T₄ and FT₄. In the 27 patients where a TRH was carried out, an hyperdynamic TSH response from a normal basal TSH level was found in two patients who each exhibited a low T₄ and a low FT₄ (Table III). Another patient had an elevated peak TSH of 27.2 mU/l after TRH and a basal value of 21.7 mU/l; this patient was aged 85 years, had a low T₄ and a low FT₄. In three further patients there were some unusual features to their TRH test but in each case T₄ was low but FT₄ normal. The response was borderline in one, hypothalamic in another and normal in the third despite an elevated basal value. In another the screening TSH was 7.0 mU/l but when the TRH test was carried out the basal TSH (3.5 mU/l) and response were normal; this patient had a low T₄ but normal FT₄. The Crooks-Wayne index of hypothyroidism would have diagnosed definite hypothyroidism in one patient and doubtful hypothyroidism in another (Table III).

As a prediction of a hyperdynamic TRH response, FT₄ was 21%, TSH 20% and T₄ 11% accurate. The sensitivity of each test for a hyperdynamic TSH response to TRH was 100% for FT₄ and T₄ but only 33% for TSH.

Discussion

Both DPH and CBZ have been shown to decrease the serum levels of T₄, free thyroxine index and FT₄.⁴⁻¹² VAL has been less intensively investigated and found to decrease T₄ and FT₄ though to a lesser degree and some have reported no consistent change.⁶⁻¹³ Our study shows that a normal T₄ and FT₄ are found in significantly more patients on VAL compared with CBZ or DPH.

Although all three anticonvulsants cause displacement of T₄ from thyroid binding globulin,¹⁴ this does not appear to be the major reason for the depression of serum thyroid hormone levels. For instance, it has been estimated that DPH given to man in therapeutic dosages is about ten times more effective in lowering the serum T₄ than would be predicted from its in vitro potency for displacing T₄ from its serum binding sites.¹⁵ It is now thought that the major determinant in the case of CBZ and DPH is accelerated hormone clearance due to hepatic enzyme

Table 1  Details of patients studied

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Male (%)</th>
<th>Age (years)</th>
<th>Daily drug dose (mg)</th>
<th>Drug level (μmol/l)</th>
<th>Usual therapeutic levels (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>20</td>
<td>50</td>
<td>27 ± 13 (15–58)</td>
<td>972 ± 476 (500–2500)</td>
<td>388 ± 206 (190–800)</td>
<td>300–900</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>20</td>
<td>50</td>
<td>32 ± 16 (13–63)</td>
<td>594 ± 298 (300–1400)</td>
<td>29 ± 13 (12–58)</td>
<td>25–42</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>31</td>
<td>52</td>
<td>40 ± 20 (16–85)</td>
<td>304 ± 95 (150–500)</td>
<td>44 ± 30 (10–129)</td>
<td>40–80</td>
</tr>
</tbody>
</table>

¹Mean ± 1 s.d. Range in parenthesis.
Table II  Initial assessment of thyroid function

<table>
<thead>
<tr>
<th></th>
<th>Valproate</th>
<th>Carbamazepine</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>$T_4$ (nmol/l)</td>
<td>$89 \pm 12$</td>
<td>$68 \pm 18$</td>
<td>$73 \pm 16$</td>
</tr>
<tr>
<td>(70–116)</td>
<td>(31–99)</td>
<td>(40–110)</td>
<td></td>
</tr>
<tr>
<td>$FT_4$ (pmol/l)</td>
<td>$14.4 \pm 3.3$</td>
<td>$11.2 \pm 3.1$</td>
<td>$11.7 \pm 2.7$</td>
</tr>
<tr>
<td>(7.8–23.3)</td>
<td>(3.7–16.8)</td>
<td>(6.6–16.7)</td>
<td></td>
</tr>
<tr>
<td>$TSH$ (mU/l)</td>
<td>$3.2 \pm 1.2$</td>
<td>$2.2 \pm 1.3$</td>
<td>$2.6 \pm 1.1$</td>
</tr>
<tr>
<td>(1.2–5.5)</td>
<td>(1.7–6.4)</td>
<td>(1.2–4.9)</td>
<td></td>
</tr>
</tbody>
</table>

$T_4$ VAL vs CBZ $P < 0.001$  
$FT_4$ VAL vs CBZ $P < 0.001$  
VAL vs DPH $P < 0.001$  
TSH No significant difference between groups

Mean ± 1 s.d. Range in parenthesis.

Table III  TRH tests, Crooks-Wayne diagnostic index and thyroid autoantibody results

<table>
<thead>
<tr>
<th>TRH test</th>
<th>Thyroid antibodies</th>
<th>Crooks-Wayne Diagnostic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TSH values in mU/l at 0, 20, 60 min)</td>
<td>Cytoplasmic</td>
<td>Thyroglobulin</td>
</tr>
</tbody>
</table>

| Indicated | Performed | Results (Sex) | Cytoplasmic | Thyroglobulin | All euthyroid  

Valproate  
4 (20%)  
3 All normal  

Carbamazepine  
13 (65%)  
11 9 normal  
2 hyperdynamic  
3.9/27.4/13.2 (M)  
3.5/25.1/17.5 (F)  
Neg  
Neg  
Hypothyroid  
Doubtful hypothyroid  
All euthyroid

Phenytoin  
19 (61%)  
13 9 normal  
1 hyperdynamic  
21.7/27.2/25.1 (F)  
Neg  
Neg  
Euthyroid  
Euthyroid  
Euthyroid  
Euthyroid  
Euthyroid

1 unusual  
6.0/16.5/13.2 (M)  
Neg  
Neg  
Euthyroid

1 borderline  
3.0/20.3/15.2 (M)  
Neg  
Neg  
Euthyroid

1 hypothalamic  
2.7/14.4/18.3 (F)  
Pos  
Neg  
Euthyroid
induction.\textsuperscript{2, 10, 15–17} Assessment of antipyrine clearance and urine \(d\)-glucaric acid excretion has indicated that CBZ and DPH induce hepatic microsomal enzymes in a marked and dose-dependent fashion whereas VAL has no significant effect.\textsuperscript{18} Therefore, unlike CBZ and DPH which are stereochromically related,\textsuperscript{19} VAL appears to have minimal hepatic enzyme induction properties and hence the mechanism by which it may lower \(T_4\) and FT\(_4\) is still uncertain.

In animal and tissue culture studies DPH may also affect hypothalamic TRH and pituitary TSH release\textsuperscript{20} and some human studies have shown a significant rise of basal serum TSH with CBZ or DPH therapy although in most cases TSH remains just within the normal reference range.\textsuperscript{24} In the series of Fichsel and Knopfle,\textsuperscript{3} 4 out of 50 children on diverse anticonvulsants had an exaggerated response to TRH, three of whom had a hypothalamic type of response.

In this study, if serum \(T_4\) alone had been used as a screening test of thyroid function then about 60% of those treated with DPH or CBZ and 15% of those on VAL would have had a subnormal value necessitating further thyroid investigation. The use of a clinical score such as the Crooks-Wayne index would only have diagnosed one patient as definitely hypothyroid and another as doubtful hypothyroid. The addition of basal serum TSH would have supported the possibility of hypothyroidism in just 4 patients, only one of whom was conclusively hypothyroid on a TRH test. An hyperdynamic TRH response was a feature in 2 other patients neither of whom had an abnormal basal serum TSH level. Basal serum TSH was also normal in the patient with a hypothalamic TRH response and in the subjects with a borderline hyperdynamic TRH response. Hence the addition of basal serum TSH in the screening of anticonvulsant treated epileptics does not appear to provide much additional information.

Free \(T_3\) was abnormal in about one-third of those on CBZ and DPH and in 5% of those treated with VAL. We found that in no single case was a reduction in FT\(_4\) associated with a normal \(T_4\). Neither of the 2 patients with a low \(T_4\) but normal FT\(_4\) required thyroid replacement therapy on biochemical or clinical grounds. Each of the 3 patients, who on clinical grounds and TRH evaluation would require thyroxine replacement, also had a subnormal FT\(_4\). Hence the use of serum FT\(_4\) would appear to be the most efficient screening test for hypothyroidism in this group of patients. The use of FT\(_4\) alone would have reduced the number of TRH tests by 60% representing not only a considerable financial saving, but also a saving of medical effort, patient inconvenience and a reduced risk of the rare but still significant danger of cardiac collapse following TRH.

Acknowledgements
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References


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