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 (T_4), free thyroxine (FT_4) 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. T_4 was found to be normal in 85% on VAL, 40% on CBZ and 39% on DPH. FT_4 was normal in more patients, namely 95% on VAL, 70% on CBZ and 65% on DPH. The TRH tests indicated that FT_4 was the most efficient screening test for hypothyroidism in this epileptic population. We estimate that the use of FT_4 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.¹ Despite a reduction in serum total thyroxine (T_4) and free thyroxine (FT_4) 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^{2–4} and cases of reversible hypothyroidism induced by phenytoin [diphenyl-hydantoin (DPH)] and carbamazepine (CBZ) have also been reported.⁵ 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 (T_4) by polyethylene glycol precipitated in-house radioimmunoassay, TSH by double antibody in-house radioimmunoassay and free thyroxine (FT_4) by a commercial 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 μ g TRH (Roche). Our reference range for T_4 is 75 to 145 nmol/l, for FT_4 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

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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 T_4 and FT_4 level which was significantly lower than those treated with VAL (Table II). Significantly more patients in the VAL group had a serum T_4 and FT_4 within the normal reference range; 85% of those on VAL had a normal T_4 as compared with 40% on CBZ ($P < 0.001$) and 39% on DPH ($P < 0.001$). A normal FT_4 was found more often than a normal T_4 ; 95% of those on VAL had a normal FT_4 compared with 70% on CBZ ($P < 0.01$) and 65% on DPH ($P < 0.01$). All the patients with a low FT_4 also had a low T_4 . 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 T_4 in all of them, because of a low FT_4 in 2 and because of a basal TSH of 5.9 mU/l in one subject, although she had a normal T_4 and FT_4 . 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 T_4 and a low FT_4 (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 T_4 and a low FT_4 . In three further patients there were some unusual features to their TRH test but in each case T_4 was low but FT_4 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 T_4 but normal FT_4 . 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, FT_4 was 21%, TSH 20% and T_4 11% accurate. The sensitivity of each test for a hyperdynamic TSH response to TRH was 100% for FT_4 and T_4 but only 33% for TSH.

Discussion

Both DPH and CBZ have been shown to decrease the serum levels of T_4 , free thyroxine index and FT_4 .⁶⁻¹² VAL has been less intensively investigated and found to decrease T_4 and FT_4 though to a lesser degree and some have reported no consistent change.^{3,8,13} Our study shows that a normal T_4 and FT_4 are found in significantly more patients on VAL compared with CBZ or DPH.

Although all three anticonvulsants cause displacement of T_4 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 T_4 than would be predicted from its *in vitro* potency for displacing T_4 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

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

[†]Mean ± 1 s.d. Range in parenthesis.

Table II Initial assessment of thyroid function

	Valproate	Carbamazepine	Phenytoin
<i>n</i>	20	20	31
T ₄ (nmol/l)	89 ± 12 (70–116)	68 ± 18 (31–99)	73 ± 16 (40–110)
FT ₄ (pmol/l)	14.4 ± 3.3 (7.8–23.3)	11.2 ± 3.1 (3.7–16.8)	11.7 ± 2.7 (6.6–16.7)
TSH (mU/l)	3.2 ± 1.2 (1.2–5.5)	2.2 ± 1.3 (1.7–6.4)	2.6 ± 1.1 (1.2–4.9)
T ₄ VAL vs CBZ <i>P</i> < 0.001	FT ₄ VAL v. CBZ <i>P</i> < 0.01	TSH No significant difference between groups	
VAL vs DPH <i>P</i> < 0.001	VAL v. DPH <i>P</i> < 0.01		
DPH vs CBZ not significant	DPH v. CBZ not significant		

Mean ± 1 s.d. Range in parenthesis.

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

TRH test (TSH values in mU/l at 0, 20, 60 min)					Thyroid antibodies			Crooks-Wayne Diagnostic Index	
	Indicated	Performed	Results (Sex)		Cytoplasmic	Thyroglobulin			
Valproate	3 (20%)	3 All normal	—					All euthyroid	
Carbamazepine	11 (65%)	11 9 normal 2 hyperdynamic	3.9/27.4/13.2 (M) 3.5/25.1/17.5 (F)		Neg	Neg		All euthyroid	
Phenytoin	13 (61%)	13 9 normal 1 hyperdynamic 1 unusual 1 borderline 1 hypothalamic	21.7/27.2/25.1 (F) 6.0/16.5/13.2 (M) 3.0/20.3/15.2 (M) 2.7/14.4/18.3 (F)		Neg	Neg		Doubtful hypothyroid	
					Neg	Neg		Euthyroid	
					Neg	Neg		Euthyroid	
					Pos	Neg		Euthyroid	

induction.^{2,10,15-17} Assessment of antipyrine clearance and urine D-glucuronic 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.¹⁸ Therefore, unlike CBZ and DPH which are stereochemically related,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 release²⁰ 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.²⁴ In the series of Fichsel and Knopfle,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_4 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.

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References

1. Ramsay, I. Drug and non-thyroid induced changes in thyroid function tests. *Postgrad Med J* 1985, **61**: 375-377.
2. Molholm Hansen, J., Skovsted, L., Lauridsen, U.B., Kirkegaard, C. & Siersback-Nielsen, K. The effect of diphenylhydantoin on thyroid function. *J Clin Endocrinol Metab* 1974, **39**: 785-789.
3. Fichsel, H. & Knopfle, G. Effects of anticonvulsant drugs on thyroid hormones in epileptic children. *Epilepsia* 1978, **19**: 323-336.
4. Rouso, I., Pharmakiotis, A., Gatzola, M., Karatza, E. & Sklavounou-Tsouroutsoglou, S. Effects of phenobarbital, diphenylhydantoin and carbamazepine on thyroid function in epileptic children. *Acta Endocrinol* 1984, **265** (suppl): 48-49.
5. Aanderud, S. & Strandjord, R.E. Hypothyroidism induced by anti-epileptic therapy. *Acta Neurol Scand* 1980, **61**: 330-332.
6. Liewendahl, K. & Majuri, H. Thyroxine, triiodothyronine and thyrotropin in serum during long-term diphenylhydantoin therapy. *Scand J Clin Lab Invest* 1976, **36**: 141-144.
7. Rootwelt, K., Ganes, T. & Johannessen, S.I. Effect of carbamazepine, phenytoin and phenobarbitone on serum levels of thyroid hormones and thyrotropin in humans. *Scand J Clin Lab Invest* 1978, **38**: 731-736.
8. Liewendahl, K., Majuri, H. & Helenius, T. Thyroid function tests in patients on long-term treatment with various anticonvulsant drugs. *Clin Endocrinol* 1978, **8**: 185-191.
9. Cavalieri, R.R., Gavin, L.A., Wallace, A., Hammond, M.E. & Cruse, K. Serum thyroxine, free T_4 , triiodothyronine and reverse- T_3 in diphenylhydantoin-treated patients. *Metabolism* 1979, **28**: 1161-1165.
10. Strandjord, R.E., Aanderud, S., Myking, O.L. & Johannessen, S.I. Influence of carbamazepine on serum thyroxine and triiodothyronine in patients with epilepsy. *Acta Neurol Scand* 1981, **63**: 111-121.
11. Yeo, P.P.B., Bates, D., Howe, J.G. *et al.* Anticonvulsants and thyroid function. *Br Med J* 1978, **1**: 1581-1583.
12. Franklyn, J.A., Sheppard, M.C. & Ramsden, D.B. Measurement of free thyroid hormones in patients on long-term phenytoin therapy. *Eur J Clin Pharmacol* 1984, **26**: 633-634.
13. Bentsen, K.D., Gram, L. & Veje, A. Serum thyroid hormones and blood folic acid during monotherapy with carbamazepine or valproate. *Acta Neurol Scand* 1983, **67**: 235-241.
14. Oppenheimer, J.H. & Tavernetti, R.R. Studies on the thyroxine-diphenylhydantoin interaction: effect of 5,5'-diphenylhydantoin on the displacement of L-thyroxine

- from thyroxine-binding globulin. *Endocrinology* 1962, **71**: 496–504.
15. Larsen, P.R., Atkinson, A.J., Wellmann, H.N. & Goldsmith, R.E. The effect of diphenylhydantoin on thyroxine metabolism in man. *J Clin Invest* 1970, **49**: 1266–1279.
 16. Aanderud, S., Myking, O.L. & Strandjord, R.E. The influence of carbamazepine on thyroid hormones and thyroxine binding globulin in hypothyroid patients substituted with thyroxine. *Clin Endocrinol* 1981, **15**: 247–252.
 17. Connell, J.C.M., Rapeport, W.G., Gordon, S. & Brodie, M.J. Changes in circulating thyroid hormones during short-term hepatic enzyme induction with carbamazepine. *Eur J Clin Pharmacol* 1984, **26**: 453–456.
 18. Perucca, E., Hedges, A., Makki, K.A., Ruprah, M., Wilson, J.F. & Richens, A. A comparative study of the relative enzyme inducing properties of anticonvulsant drugs in epileptic patients. *Br J Clin Pharmacol* 1984, **18**: 401–410.
 19. Rootwelt, K., Ganes, T. & Johannessen, S.I. Effect of carbamazepine, phenytoin and phenobarbitone on serum levels of thyroid hormones and thyrotropin in humans. *Scand J Clin Lab Invest* 1978, **38**: 731–736.
 20. Smith, P.J. & Sarks, M.I. Multiple effects of 5'5'-diphenylhydantoin on the thyroid hormone system. *Endocrine Reviews* 1984, **5**: 514–524.