

## SHORT REPORT

## Carbamazepine, serum thyroid hormones and myocardial function in epileptic patients

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### Abstract

**Serum thyroid hormone and thyrotropin levels were assayed and the myocardial function was evaluated by measuring systolic time intervals both in 30 patients with epilepsy on long-term carbamazepine monotherapy and in 19 healthy volunteers. Serum thyroxine, free thyroxine and triiodothyronine levels were significantly lower ( $p < 0.001$ ) in the patient group than in the control group and systolic time intervals were similar in both groups.**

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Since the original report of Oppenheimer *et al*<sup>1</sup> on the depression of serum protein bound iodine in epileptic patients treated with phenytoin, the changes in serum thyroid hormone levels during the use of antiepileptic drugs have been widely investigated.

Carbamazepine and phenytoin seem to have a similar effect on thyroid function: serum thyroxine (T<sub>4</sub>) and free thyroxine concentrations decrease, but serum thyrotropin (TSH) levels remain unchanged.<sup>2-4</sup> However, serum triiodothyronine (T<sub>3</sub>) levels have not been found to be decreased as consistently as serum T<sub>4</sub> and FT<sub>4</sub> concentrations during carbamazepine medication.<sup>2,3</sup> Serum T<sub>4</sub> and/or FT<sub>4</sub> levels decrease below the normal range after just two months therapy with carbamazepine in approximately 50% of patients, and remain at a similarly low level during long-term treatment.<sup>2</sup> However, patients appear clinically euthyroid during carbamazepine medication.

Hypothyroidism leads to abnormalities in cardiac structure and function, and the severity of myocardial dysfunction seems to correlate with the grade of hypothyroidism.<sup>5</sup> Measurement of systolic time interval (STI), a measure of myocardial function,<sup>6</sup> shows a pattern characteristic of depressed myocardial contractility in hypothyroid patients.<sup>5</sup>

The present study aimed to evaluate whether patients with epilepsy receiving long-term carbamazepine medication reveal signs of myocardial dysfunction in STI correlating to hypothyroidism.

### Methods

The study was approved by the ethical committee of the Medical Faculty of the University of Oulu. The principles of the Declaration of Helsinki were followed.

Thirty outpatients with idiopathic epilepsy participated in the study after giving their informed consent. The mean (SD) age of the patients was 23.6 (3.4) years. There were 15 male patients [mean (SD) age 23.8 (3.8) years], and 15 female patients [mean (SD) age 23.4 (3.2) years]. All patients had carbamazepine monotherapy as their antiseizure medication and the therapeutic regime had been unaltered for at least one year before the study. The mean (SD) duration of carbamazepine medication of these patients was 4.9 (2.9) years, the mean (SD) daily carbamazepine dose 509 (104) mg, and the mean (SD) serum level of carbamazepine 24.2 (5.0)  $\mu\text{mol/L}$ . The seizure control was in most cases good: 19 patients had had no seizures during the medication, four patients had less than one seizure per year, six patients had more than one seizure per year but less than one seizure per month, and one patient had more than one monthly seizure.

All patients were studied by the same person (MR) to evaluate the thyroid, cardiovascular and neurological status. Patients showing any symptoms or signs of illnesses other than epilepsy, and female patients who were pregnant, lactating, or receiving contraceptive pills, were excluded.

Nineteen healthy volunteers with a mean (SD) age of 25.1 (3.3) years served as control subjects. There were 9 male [mean (SD) age 26.0 (3.3) years] and 10 female control subjects [mean SD age 24.0 (3.0) years].

The blood samples of patients and controls were drawn and the STI performed in the morning at 8.00 am after an overnight fast and before the morning dose of the medication was taken. All patients had been seizure-free for at least two weeks before entering the study.

### Assays

Serum T<sub>4</sub> and T<sub>3</sub> concentrations were analysed by radioimmunoassay methods using reagent kits from Farnos Diagnostica (Turku, Finland). The sensitivity of the T<sub>4</sub>

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Table Serum hormone concentrations and STI of patients on long-term carbamazepine medication and of control subjects. Values are means (1 SD).

	Patients n = 30	Control subjects n = 19	Statistics
T4 (nmol/L)	65.9 (13.7)	90.6 (18.8)	p < 0.001
FT4 (pmol/L)	12.5 (2.0)	17.0 (2.1)	p < 0.001
T3 (nmol/L)	1.7 (0.2)	2.0 (0.3)	p < 0.001
TSH (mU/L)	2.4 (1.3)	1.8 (0.7)	NS
PEP (msec)	104.0 (12.8)	108.0 (14.7)	NS
LVET (msec)	306.5 (22.7)	305.6 (18.3)	NS
PEP/LVET	0.34 (0.04)	0.35 (0.05)	NS

T4, thyroxine; FT4, free thyroxine; T3, triiodothyronine; TSH, thyrotropin; PEP, pre-ejection period; LVET, left ventricular ejection time.

assay was 5 nmol/L, the coefficient of intra-assay variation was 4.5%, and that of inter-assay variation was 5.7%. The respective values for T3 assay were 0.1 nmol/L, 5.1%, and 6.2%. Serum TSH concentrations were determined by a fluorimetric method using reagent kits from Wallac Corp (Turku, Finland). The sensitivity of the assay was 0.03 mU/L. The intra-assay variation was 5.4% and the interassay variation was 6.0%. Serum FT4 concentrations were measured using radioimmunoassay kits obtained from Diagnostic Products Corp (Los Angeles, Ca, USA). The sensitivity was 0.13 pmol/L, the intra-assay variability was 4.4%, and the interassay variability 5%. Serum carbamazepine concentrations were assayed by a fluorescence polarisation immunoassay system using an analyser (TDX, Abbott Diagnostic Division, Irving, Texas, USA). The sensitivity of the assay was 2.1 µmol/L, the intra-assay variation was 1.5%, and the interassay variation was 2.5%.

#### Measurement of STI

STI were measured using Hewlett-Packard contact transducers 21050 A (Andover, Ma, USA) and a multichannel ultraviolet recorder with 150 mm/sec paper speed using a standard technique.<sup>8</sup> Measurements were averaged over 10 consecutive cardiac cycles without knowledge of the subject's clinical data.

#### Results

The serum T4, FT4, and T3 concentrations were significantly lower (t test p < 0.001) in the patient group than in the control group (table). No statistically significant differences were found in the serum TSH concentrations between these two groups. The STI (pre-ejection period, PEP; left ventricular ejection time, LVET; PEP/LVET) were similar in the patient and the control groups.

All patients were clinically euthyroid. Six of the patients complained of fatigue and/or minor memory disturbances.

#### Discussion

Carbamazepine is a known inducer of the hepatic microsomal enzyme system,<sup>9</sup> and as previously suggested,<sup>10</sup> increased degradation of thyroid hormones in the liver is probably responsible for the decrease in serum thyroid hormone concentrations during CBZ medication.

But are the carbamazepine treated patients suffering from a sort of hypothyroid state or not? Subclinical hypothyroidism is nowadays a well known entity, characterised by relatively few clinical and biochemical abnormalities, and is defined solely by elevations in circulating TSH levels with serum thyroid hormone concentrations within the normal range.<sup>11</sup> In patients on carbamazepine medication serum TSH levels do not increase, that is, the positive feedback mechanism due to low serum thyroid hormone concentrations is not activated and serum thyroid hormone levels remain low. Moreover, TRH stimulated secretion of TSH is not increased, either, during carbamazepine medication.<sup>2</sup> It is possible therefore that either long-term carbamazepine therapy disturbs hypothalamic function or a new steady state of thyroid hormone balance develops during carbamazepine medication.

It has, however, previously been found to be very difficult to assess thyroid hormone effects at the tissue level in patients on antiepileptic drugs. Kodama *et al.*,<sup>12</sup> evaluated the basal metabolic rate (BMR) in epileptic children with low serum thyroid hormone levels treated with antiepileptic drugs. The patients were on polytherapy. BMR values were found to be low in some patients, but T4 replacement therapy had no improving effect on BMR values in most cases. Furthermore, Herman *et al.*,<sup>13</sup> evaluated BMR and thyroid function in carbamazepine treated patients with depression. Carbamazepine had no significant effect on BMR despite robust decreases in serum thyroid hormone concentrations.

It has been shown that thyroid hormones have a major role in the maintenance of normal left ventricular structure and function.<sup>14</sup> Measurement of STI evaluates myocardial function.<sup>8</sup> PEP prolongation, LVET shortening, and PEP/LVET increase is a pattern of STI which is characteristic of depressed myocardial contractility, and this pattern of STI has also been found in hypothyroid patients.<sup>5,7,15</sup>

The STI of our patients with epilepsy receiving long-term carbamazepine medication did not differ from the STI of the control subjects, although the serum thyroid hormone concentrations were significantly lower in the patient group.

The decrease in serum thyroid hormone levels commonly seen in patients with epilepsy during carbamazepine medication is not severe enough to change the myocardial function of these patients.

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