

Antiepileptic Drugs and Thyroid Function

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ABSTRACT

Antiepileptic drugs (AED) are a heterogeneous group of compounds widely used in both adults and children. These drugs are related to various adverse effects involving several organs and endocrinological and metabolic functions. In particular, relevant effects on thyroid function have been described. Subclinical hypothyroidism and alterations in thyroid hormone serum levels are reported in the literature; phenytoin, valproate and carbamazepine, in particular, seem to be involved in these alterations. The aim of this review is to analyse critically the principal alterations in thyroid function caused by AED therapy.

KEY WORDS

epilepsy, thyroid function, phenytoin, valproate, carbamazepine

INTRODUCTION

Treatment with antiepileptic drugs (AED) is associated with multiple short- and long-term effects. Effects on endocrine function, in particular, alteration of thyroid function, is an example of these side effects. Many AEDs may alter thyroid hormone homeostasis at the level of biosynthesis, release, transport, metabolism and excretion of thyroid hormones.

In 1961, Oppenheimer *et al.*¹ first reported changes in serum thyroid hormone levels in pheny-

toin (PHT)-treated epilepsy patients who had a depression of serum protein-bound iodine; since then, the interaction between thyroid hormones and AEDs has been investigated extensively and a sizeable literature focusing on thyroid function and AEDs has been produced over the last years; it has also been suggested that some AEDs may induce subclinical hypothyroidism.

The purpose of the present review is to evaluate in depth the data from the literature and to clarify the link between AEDs and thyroid function.

ANTIEPILEPTIC DRUGS

Barbiturates

Barbiturates enhance gamma-aminobutyric acid (GABA)-mediated increases in chloride conductance by prolonging the duration of channel opening². Very few reports have been shown on the correlation between barbiturates and the thyroid. Phenobarbital is a barbiturate widely used as an anticonvulsant and sedative drug, long recognized as a potent inducer of hepatic microsomal enzymes in both man and rat: induction generally refers to isozymes of the cytochrome P450 system³.

Cavlieri *et al.*⁴ demonstrated that in hyperthyroid patients with Graves' disease on phenobarbital treatment, thyroxine (T4) values decreased. Later, another study⁵ showed decreased serum T4 levels with thyroid stimulating hormone (TSH) minimally depressed. The fact that TSH did not increase suggests that the overall effect of therapeutic levels of phenobarbital on human thyroid hormone metabolism is relatively mild³.

Benzodiazepines

The most common used benzodiazepines are clonazepam, diazepam and lorazepam. These act at distinct allosteric binding sites on the GABA_A receptor-chloride ionophore to enhance GABA-

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mediated increases in chloride conductance⁶. Thyroid hormones are involved in the occurrence of anxiety and affective disorders; however, the effects following an anxiolytic benzodiazepine treatment on the mechanism of action of thyroid hormones has not yet been investigated. Only one study⁷ has reported the effect of diazepam on nuclear triiodothyronine (T3) binding, as well as on the relative expression of thyroid hormone receptors and on synaptosomal thyroid hormone availability in adult rat cerebral hemisphere 24 h after a single intraperitoneal of this tranquillizer. Although diazepam did not affect the availability of thyroid hormones either in the blood or in the synaptosomal fraction, it decreased nuclear T3 maximal binding density. The same study showed that a single intraperitoneal injection of diazepam affects, within 24 h, the density of the nuclear thyroid hormone receptors and their expression pattern.

Carbamazepine

Carbamazepine (CBZ) is a widely used AED for partial and generalized tonic-clonic seizures. Its mechanism of action is to inhibit high-frequency neuronal firing by blocking voltage-gated sodium channels⁸.

CBZ is an anticonvulsant drug with a well documented effect on thyroid metabolism⁹⁻¹². In 1978, Liewendahl *et al.*⁹ first reported decreases in T4 and free thyroxine (FT4) concentrations, with TSH levels unchanged during CBZ treatment. From this study many reports with the aim to evaluate serum thyroid hormone balance in children receiving long-term therapy with CBZ were proposed. Isojarvi *et al.*¹³ and Eiris-Punal *et al.*¹⁴ suggested that CBZ may induce subclinical hypothyroidism.

CBZ therapy has certain effects on thyroid function: it decreases serum thyroid hormone levels, but serum thyrotropin (TSH) concentrations and TSH responses to thyrotropin-releasing hormone remain normal^{5,15}. A decrease in serum thyroid hormone levels can already be detected in patients 2 months after starting CBZ¹⁶. The large majority of these studies have demonstrated that in adult patients, serum T4 and FT4 decrease whereas

TSH levels remain unchanged. The effects of CBZ on thyroid function appear to be more complex than can be attributed to a single action of the drug. The altered thyroid function during CBZ medication has been attributed to induction of the hepatic P450 enzyme system and the consequent increase in the metabolism of thyroid hormones^{11,17}. The ability of the thyroid to compensate for suboptimal levels of thyroid hormones can be limited.

Verrotti *et al.*¹⁵ demonstrated changes in serum thyroid hormone levels in 37 children with epilepsy during CBZ and valproic acid (VPA) therapy. Serum T4 and FT4 levels were significantly lower in patients treated with CBZ and CBZ + VPA than in the controls. These data suggest that children treated with CBZ may have subclinical signs of hypothyroidism and these changes are more evident if CBZ is given in association with VPA. TSH and thyrotropin-releasing hormone levels did not seem to be affected by these drugs, suggesting that hypothalamic function is not affected in these children.

The aim of another study¹⁸ was to analyze whether thyroid dysfunction encountered in patients with epilepsy would also be associated with an abnormal lipid profile. In this study and consistent with many others, 28.4% (25/88) patients with epilepsy had serum FT4 levels below the reference control range. The risk was increased among CBZ-treated patients with epilepsy (76% [19/25]). Hamed *et al.*¹⁸ noted enlargement of the thyroid gland and the presence of thyroid cysts in 20% of the CBZ-treated patients. However, data have demonstrated that the changes induced by this drug are transient¹⁵.

While CBZ decreases thyroid hormone concentrations it rarely causes hypothyroidism. A very recent study by Simko and Horacek¹⁹ assessed prospectively the early effect of CBZ on thyroid status in thyroxine-supplemented hypothyroid patients, when compared with patients without thyroid disorders. Patients with no thyroid disorder (group A) were compared with thyroxine-supplemented hypothyroid patients, stable before CBZ treatment (group B). In group A, T4 decreased significantly starting from the first week, while TSH increased only slightly, never exceeding the

normal range. In group B, a similar T4 and FT4 decline was followed by significantly increasing TSH. In conclusion this study demonstrated that in patients with no thyroid disorder, CBZ causes hormonal changes of no clinical relevance, due to adaptive response. In T4-supplemented hypothyroid patients this adaptation is lacking; CBZ may precipitate subclinical or overt hypothyroidism, and early thyroid function monitoring seems advisable.

Oxcarbazepine

Oxcarbazepine (OXC) is an AED indicated as first-line therapy for the treatment of partial and secondarily generalized tonic-clonic seizures²⁰. OXC has properties similar to those of CBZ; it blocks sodium channels and interrupts high-frequency repetitive firing of neurons²¹. The metabolic pathway of OXC in the liver is different from that of CBZ, consequently OXC does not appear to induce the hepatic P450 enzyme system²², but no high doses were studied. Although OXC is widely used in the treatment of partial epilepsy, there are only a few studies focused on its effects on thyroid functions.

Isojarvi *et al.*²³ demonstrated that both CBZ- and OXC-treated men with epilepsy had low serum T4 and FT4 concentrations. However, in both of these patient groups, serum T3 and TSH were normal. The low serum T4 and FT4 concentrations in OXC-treated men were similar to those of men taking CBZ, and as with the CBZ-treated patients, OXC-treated men also had normal levels of serum T3 and TSH. This is the first study on thyroid function in patients taking long-term OXC medication.

Vainionpaa *et al.*¹² evaluated thyroid function in 78 girls taking CBZ, OXC or VPA monotherapy for epilepsy (18 taking OXC). In the first evaluation, the mean serum thyroid hormone concentrations were lower in the girls taking CBZ or OXC. However, TSH concentrations were normal in the girls taking CBZ or OXC, and 67% of the girls taking OXC had serum T4 and/or FT4 levels below the lower limit of the reference range. In conclusion, this study suggested that OXC reduces serum thyroid hormone concentrations in girls with epilepsy and the changes in serum

thyroid hormone are reversible after withdrawal of the medication.

In a recent study, Cansu *et al.*²⁴ evaluated the effects of short-term OXC monotherapy on thyroid functions in children. In these patients T4, FT4, T3 and free triiodothyronine (FT3) levels were found to be decreased at the third and the sixth months, while TSH remained in the normal range throughout the study. In conclusion, in this study it is documented that children under short-term OXC therapy showed altered thyroid functions similar to the changes observed after long-term treatment.

Gabapentin

Gabapentin is a cyclic GABAergic analog and acts as a GABA agonist²⁵. It is not metabolized and is excreted unchanged in urine^{26,27}, but the GABAergic mechanism is not completely known. In the literature, a 17 year-old female was reported with elevated TSH level during gabapentin treatment³. Moreover, Frye *et al.*²⁸ reported a woman who developed thyroiditis. Upon gabapentin discontinuation there was prompt resolution of symptoms and a return to her baseline thyroid function.

Lamotrigine

Lamotrigine (LTG) is emerging as a clinically useful AED in the treatment of refractory partial epilepsy, generalized seizures, typical absence seizures, and Lennox-Gastaut syndrome^{29,30}. Positive clinical trials with LTG have also been reported for the treatment of mania bipolar disorder³¹⁻³⁴, neuropathic pain^{35,36}, migraine attacks with aura³⁷, and Huntington's disease³⁸. Experimental evidence supports the view that the principal mechanism of action of LTG is blockade of both voltage-gated sodium (Na⁺) and calcium (Ca²⁺) channels³⁹⁻⁴⁴ although other actions have been proposed⁴⁴.

No effects on thyroid function have been reported and LTG is reported as not exhibiting auto-induction⁴⁵⁻⁴⁷. In two reviews^{48,49}, LTG is presented as an inducer. Indeed LTG can decrease valproate plasma levels⁵⁰. In a study by Goodwin *et al.*⁵¹, bipolar I patients were treated with LTG (n = 280; 50-400 mg/day fixed dose or 100-400 mg/day flexible dose), lithium or placebo. TSH was

elevated in the lithium (8%) and placebo (<1%) groups but not in the LTG group.

Levetiracetam

Levetiracetam (LEV) is an analog of piracetam and was recently proven effective as adjunctive therapy and very well tolerated in controlling refractory partial seizures in adults⁵². The main cellular mechanisms thought to account for the anti-seizure activities consist either in facilitation of inhibitory GABAergic neurotransmission⁵³ and inhibition of excitatory glutamate receptors or blockage of voltage-gated Na⁺ or Ca²⁺ channels⁵⁴. No effects on thyroid function have been reported³.

Phenytoin

Phenytoin (PHT) was introduced for the treatment of epilepsy in 1938⁵⁵. The success of PHT as an anticonvulsant was one of the major pharmacological advances in treating neurological diseases and favourably altered the lives of many people with epilepsy worldwide. PHT produces effective anticonvulsant action without troublesome sedation, and it is one of the most effective compounds for treating generalized tonic-clonic seizures^{56,57} and status epilepticus^{58,59}.

Thyroid function is involved in chronic toxicity of PHT. A significant depression in thyroid hormone serum levels is present in all patients who received PHT^{9,13,18,60-72}. The decline of serum protein iodine sometimes induced by PHT is probably related to changes in protein binding of the thyroid hormones, increased clearance, and peripheral T4 to T3 conversion and a weak T3 agonist function⁶¹. Uptake of triiodothyronine and radioactive iodine by red blood cells is not altered, and most patients are clinically euthyroid. Triiodothyronine and TSH levels are usually normal. The symptoms of PHT toxicity may mimic those of hypothyroidism⁷³⁻⁷⁵.

Tiagabine

Tiagabine (HCl) is a potent blocker of GABA uptake by neurons and glia. No effects on thyroid function have been reported. In a study by Man *et al.*, CBZ-treated patients (dose 400-800 mg/day)

showed significant alterations of TSH and FT4 that were not present in HCl-treated patients (dose 10-20 mg/day). Thus HCl seemed not to affect thyroid hormones⁷⁶.

Topiramate

Topiramate (TPM) exhibits multiple mechanisms of action, a feature suggestive of a broad spectrum of anti-seizure activity. After evaluation as adjunctive therapy in adults with partial onset seizures, the development program for TPM followed a traditional route into paediatrics, secondary generalized seizures, primary generalized seizures, and more recently, monotherapy in adults and children with newly diagnosed or therapy-resistant epilepsy⁷⁷. Ben-Menachem *et al.* demonstrated that TPM added to anticonvulsant therapy (from 25-100 mg/day) caused a significant reduction in TT4 and rT3 levels, even though all thyroid parameters remained within the normal range and all patients were clinically euthyroid⁷⁸.

Valproic acid

Valproate (VPA), which was the first marketed in France over 30 years ago, has become one of the leading drugs for the treatment of various forms of epilepsy. It was recently approved for other indications, including mood disorders and migraine. VPA is probably now the AED with the best-investigated array of adverse effects, some frequent, some predictable and mostly benign, others rare and potentially severe. Many studies reported altered thyroid function (particularly low FT4) among patients with epilepsy during treatment with VPA, but the results were controversial: normal or elevated serum levels of thyroid hormones and TSH have been reported^{15,23,63,79,80}. Therefore it seems that these changes are inconsistent; although subclinical peripheral hypothyroidism in children^{14,24,81} and slightly increased TSH with normal FT4 and T4 in girls¹² have been reported. Other studies showed that thyroid hormones and TSH concentrations in a group of men on VPA therapy were normal^{13,18,23} and VPA seemed not to have significant effects on thyroid function. Many studies documented that these changes were reversed after discontinuation of VPA, and were

never associated with overt thyroid dysfunction.

Co-administration of VPA with enzyme-inducing AEDs may cause a decrease in serum levels of the thyroid hormones T3 and T4¹³.

Vigabatrin

Vigabatrin is the only AED that is a selective, irreversible GABA-transaminase inhibitor that greatly increases whole-brain levels of GABA, presumably making it more available to its receptor site⁷⁷. There are few studies that considered the hormonal effects of vigabatrin. Bianco *et al.*⁸² considered the endocrine effects of vigabatrin, CBZ and PHT used as monotherapy or in association (n = 39). Vigabatrin in association with CBZ and PHT seemed to cause lower FT4 levels and decreased TSH levels in comparison with CBZ or PHT given as monotherapy, but it was not reported whether the difference was statistically significant. The authors concluded that vigabatrin associated with CBZ and PHT reduces the risk of hypothyroidism related to the use of these drugs as monotherapy. Further studies are needed to understand the effects of vigabatrin therapy on thyroid function.

CONCLUSION

Experimental and clinical studies have shown that various AEDs can interfere with thyroid function. The underlying mechanism and clinical significance of altered serum concentrations of thyroid hormones by AEDs have remained unclear. Further studies will be useful to determine the effects of certain AEDs (i.e. lamotrigine, vigabatrin and valproate). Alteration of thyroid hormone homeostasis by phenobarbital/primidone, phenytoin and carbamazepine clearly occurs in epileptic patients during anticonvulsant therapy. However, in the majority of cases they are not associated with increased TSH. Although the treated patients did not show clinical hypothyroidism, from a practical point of view, it is possible that patients with a family or personal history of derangement in thyroid function can be considered to be at risk for these hormonal changes; therefore, these drugs should be avoided if possible in this category of children.

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