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Review

Interactions between antiepileptic drugs and hormones

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ABSTRACT

Antiepileptic drugs (AEDs) are known to have endocrine side effects in both men and women. These can affect fertility, sexuality, thyroid function, and bone health, all functions of major importance for well-being and quality of life. The liver enzyme inducing antiepileptic drugs (EIAEDs), like phenobarbital, phenytoin, and carbamazepine, and also valproate (VPA), a non-EIAED, are most likely to cause such side effects. AED treatment can alter the levels of different sex hormones. EIAEDs increase sex hormone binding globulin (SHBG) concentrations in both men and women. Over time, this elevation can lead to lower levels of bioactive testosterone and estradiol, which may cause menstrual disturbances, sexual problems, and eventually reduced fertility. VPA can cause weight gain in both men and women. In women, VPA can also lead to androgenization with increased serum testosterone concentrations, menstrual disturbances, and polycystic ovaries.

Lamotrigine has not been shown to result in endocrine side effects. The newer AEDs have not yet been thoroughly studied, but case reports indicate that some of these drugs could also be suspected to cause such effects if endocrine changes commence after treatment initiation.

It is important to be aware of possible endocrine side effects of AEDs as they can have a major impact on quality of life, and are, at least partly, reversible after AED discontinuation.

1. Introduction

Epilepsy can have major impacts on several important aspects of life. The severity of the disease varies from good seizure control or seizure freedom (50–60%) with minor side effects from medication, to a debilitating disease with several daily seizures, the need for polytherapy, the occurrence of major side effects, and problems with drug interactions. Many patients also suffer from an underlying brain disease and co-morbidity, with depression or psychiatric disorders, for example, occurring frequently.

The epilepsy itself, with frequent epileptic discharges, can interact with cerebral function and affect memory and other cognitive aspects. Alterations in hormone levels are a direct effect of epileptic discharges, both in animals and humans [1–5].

Distinguishing the side effects of antiepileptic drugs (AEDs) from the many other factors that influence the patients can be difficult. *In vitro* experimental studies, *in vivo* animal studies, and studies in humans using the same medication for diagnoses other than epilepsy, can be helpful. In order to avoid the possible complexity from multiple interactions, monotherapy studies are important.

Despite these investigative difficulties, AEDs have been clearly demonstrated to have several hormonal side effects that can influence important areas in life, such as fertility, sexual function, and bone health. Some side effects may also be of a more cosmetic nature, such as weight gain, hair loss, acne, or a more masculine hair distribution in women. The various drugs affect the hormonal system differently, and cause specific and different types of hormonal disturbances.

2. Reproductive endocrine function in men

2.1. Enzyme-inducing drugs

The AEDs phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ) are all inducers of hepatic microsomal enzymes, and thus accelerate the metabolism of other drugs, and also the breakdown and production of sex hormone binding globulin (SHBG). This increases SHBG concentrations and reduces concentrations of free, circulating androgen and estrogen, resulting in

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decreased levels of biologically active sex hormones [6–9]. Elevated estradiol levels have also been found in men with epilepsy taking PHT [7,10].

Low serum dehydroepiandrosterone sulfate (DHAES) concentrations have also been reported in men and women taking PHT and CBZ [6,8,11]. DHAES is a weak androgen that is secreted from the adrenal cortex, but the clinical implication of low DHAES levels is unknown.

Associations between high estradiol levels and sexual dysfunction have been found in men taking PHT [10]. In some men, sexual dysfunction has also been described after long-term CBZ or PHT treatment and is related to low bioactive testosterone levels [12]. Furthermore, both CBZ and PHT have been associated with changes in semen quality [13] and CBZ has been linked with reduced sperm motility and increased frequency of morphologically abnormal sperm [14,15].

Despite these findings, there is no obvious significant reduction in fertility in patients using enzyme-inducing AEDS (EIAEDs) [16].

Oxcarbazepine: Oxcarbazepine (OXC) has a different metabolic pathway to that of CBZ. Instead of oxidation, OXC is metabolized by reduction to its active metabolite, 10,11-dihydro-10-hydroxy-carbamazepine, and induces the liver P450 enzyme system only at high doses [17]. OXC taken in high doses may affect serum testosterone and SHBG levels, and may also induce changes in sperm morphology [18]. However, these findings should be confirmed in further studies before conclusions on their clinical significance can be reached.

2.2. Valproate

Valproate (VPA) does not induce liver enzymes, but, nevertheless, does reduce serum gonadotropin levels and increase concentrations of serum androstenedione [15,19]. These effects may be caused either by a centrally mediated modification of GABA-ergic neurotransmission in the hypothalamus or by a direct effect of VPA on endocrine tissue, in particular in the testis. A direct effect on the testis is supported by studies in dogs, rats, and goats that have demonstrated a reduction in testicular size and altered testicular morphology after VPA treatment [14,19,20]. Similarly, small testicular volumes have also been found in some [14], but not all [14], studies of men taking VPA. Further, semen morphology and motility are affected by VPA. In humans, the number of motile sperms is reduced, and several morphological parameters are changed [14,15]. In contrast to findings with CBZ, sperm from men that have been treated with VPA have been found to show increased tail pathology [14]. A number of studies of infertile men without epilepsy have shown these types of sperm tail abnormalities; bent or coiled sperm tails were found to occur significantly more frequently when pregnancy did not occur [20–22]. These findings suggest that sperm tail changes observed with VPA may affect fertility. Carnitine is important for sperm motility, and reduced sperm motility has been noted in men on VPA, and in whom the free *versus* total carnitine ratio is reduced [23,24].

2.3. Lamotrigine

To date, lamotrigine (LTG) has not been associated with reproductive endocrine disturbances in men with epilepsy nor in non-epileptic animals [12,25–28].

2.4. Levetiracetam

The mode of action levetiracetam (LEV) is mostly unknown, and differs from that of other AEDs. The drug binds to a synaptic vesicle protein, SV2A, which is widely distributed in the central nervous system and in most endocrine tissues. In a paper from Harden et al. [29] from 2010 testosterone levels increased in eight men after LEV treatment. However, this study was uncontrolled and included a very heterogeneous group of patients. In a clinical study by Svalheim [28], 30 men treated with LEV did not differ from controls regarding reproductive hormones or sexual function. Normal levels of sexual hormones were also found in a recent Chinese study by Xiaotian [30], but more sperm abnormalities were reported in LEV-treated males. Further studies are therefore needed before any conclusions can be drawn regarding the effects of LEV on reproductive endocrine function in men.

2.5. Topiramate

Sexual dysfunction has rarely been described in association with treatment with the newer AEDs, but there has been growing evidence of a correlation between topiramate (TPM) treatment and erectile dysfunction [31–33] and dose dependent reversible anorgasmia (both men and women) [34,35]. A non-hormonal, vasogenic mechanism has been suggested to explain these associations [33].

3. Reproductive endocrine function in women

3.1. Enzyme-inducing drugs

As in males, EIAEDs in females reduce the free fractions of steroid hormones, increase SHBG, and may also lower DHEAS. No consistent abnormalities in basal or stimulated serum gonadotropin or prolactin levels have been reported [36]. The clinical consequences of these endocrine changes are unknown. To date, no large study has demonstrated any increased frequency of menstrual disorders or other reproductive endocrine disorders in women treated with these drugs [27].

3.2. Valproate

The first report suggesting a high incidence of menstrual disorders linked to obesity, hyperandrogenism, and polycystic ovaries (PCO) in women taking VPA for epilepsy was published in 1993 by Isojärvi et al. [37]. This was a cross-sectional study of 238 women on VPA monotherapy. These women had significantly more menstrual disorders than controls, and these were frequently associated with PCO and/or hyperandrogenism. PCO and hyperandrogenism were especially common if VPA medication had been started before the age of 20 years. Moreover, the serum mean androgen levels were increased in women on VPA. These findings have been confirmed in later studies [38]. In a large, three-center study, with patients from Finland, Norway and Netherlands, hyperandrogenism and/or PCO were detected in 70% of VPA-treated women, 20% of CBZ-treated women, and 19% of women acting as controls. Menstrual disorders were reported by 59% of women on VPA, compared with 12% of CBZ-treated women and 15% women in the control group [39].

The age dependency, found by Isojärvi in 1993 [37] was later confirmed by others [38]. Furthermore, increases in serum androgen levels were detected before and during pubertal development in young girls taking VPA for epilepsy [40]. A five-year follow-up of these girls showed that of the girls/women who were still on VPA 5 years later (during the follow-up study), 60% had polycystic ovary syndrome (PCOS) as compared with 25% of the girls/women who had stopped taking VPA and switched to other AEDs [41]. These observations indicate that the young ovary is more vulnerable to the effects of VPA.

Similar endocrine changes induced by VPA were also seen in non-epileptic rats in a long-term monotherapy study [25]. A significant, dose-dependent increase in the number of follicular cysts in the ovaries was observed after VPA treatment, together with a reduction in the number of corpora lutea. Blood samples