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Review

New antiepileptic drugs and women

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ABSTRACT

Since 1990, sixteen new antiepileptic drugs (AEDs) have been introduced. Most of these new AEDs have only been insufficiently studied with respect to women-specific aspects such as endogenous sex hormones, hormonal contraception, pregnancy, breastfeeding, or menopause. This is of concern because it has been shown for some of the new AEDs that these factors may have a clinically significant impact on their pharmacokinetics and seizure control. Also, new AEDs may affect hormone homeostasis and pass over into breast milk. The best studied of the new AEDs are lamotrigine, levetiracetam and oxcarbazepine. Although gabapentin and pregabalin are even more frequently used (due to their therapeutic effects in nonepileptic conditions), our understanding of these two drugs in relation to women's issues is surprisingly poor. Little to nothing is known about zonisamide, retigabine/ezogabine, lacosamide, perampanel and the other new AEDs. Nevertheless, many small studies and case series have been published on new AEDs and women-specific aspects. This review gives an overview on what is known today.

1. Introduction

Antiepileptic drugs (AEDs) are widely used. They are prescribed as standard treatment not only for epilepsies, but for a variety of nonepileptic conditions as well, mainly bipolar spectrum disorders and chronic pain states.[1,2] In fact, only one out of three AED users takes these drugs for epilepsy.[3,4] A large number of AEDs are available. Since 1990, 16 new (or "second-generation") AEDs have been registered: lamotrigine, vigabatrin, tiagabine, felbamate, topiramate, gabapentin, pregabalin, levetiracetam, zonisamide, stiripentol, oxcarbazepine, eslicarbazepine, rufinamide, lacosamide, retigabine, and perampanel. In many countries, women constitute the majority of users of these new AEDs.[5–7] This may be due to special, women-related safety and tolerability issues, but as well to the epidemiology of certain disease states.[8,9]

During the past 20 years, much attention has been directed toward AEDs and women. Hormonal and metabolic disturbances induced by AEDs, as well as teratogenic and adverse cognitive effects in the offspring of women with epilepsy have come into the spotlight.[10–13] Other women-specific questions such as drug interactions with hormonal contraception, the menstrual cycle, pharmacokinetic changes during pregnancy, breast-feeding, and menopause have also received growing attention.[14–18] Many studies on these issues have been conducted with the classic AEDs, mainly valproate and carbamazepine. With respect to the newer antiepileptic drugs however, only lamotrigine appears to be comparably well-studied. Other new AEDs have been examined only in part, or not at all.

Generally, and with only few exceptions (e.g., felbamate and vigabatrin), the new AEDs possess favorable safety profiles compared to the classic AEDs. Especially concerning hormone-related issues and teratogenicity, the new AEDs appear to come out better than the older AEDs.[19] Accordingly, the use of new AEDs by fertile women has increased considerably.[20]

Many of the studies discussed in this review, although useful, are small and do not qualify as basis for sound clinical guidelines. Their results should be reproduced by further, and preferably larger, studies. In fact, there are still too many gaps in our knowledge and much research remains to be done. Nonetheless, this review aims to give a brief yet concise overview on what is currently known, and what is not, on the clinical pharmacokinetics of new AEDs in women. Possible effects on the offspring of women treated with new AEDs (teratogenic or cognitive) will not be covered.

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2. Sex hormones

2.1. Endogenous female sex hormones

Female sex hormones can roughly be divided into estrogens and progestogens, and both of them can be of endogenous or exogenous origin. Estrogens have long been seen as pro-convulsive compounds while progestogens are generally thought to have anti-convulsive effects.[21–25] While this implies a theoretical possibility of pharmaco*dynamic* interactions with AEDs, things are not that simple. Estrogens may have neuroprotective and anti-convulsive effects as well. Their effects may depend on the body's general hormonal state, and fluctuations in the serum level ratio between estrogens and progestogens also seem to be of great relevance for the biological effects of estrogens.[25] Thus, with our limited knowledge, any net effect of the theoretical pharmaco*dynamic* interactions between estrogens, progestogens and AEDs would be difficult to evaluate or predict.

Pharmaco*kinetic* effects of endogenous female sex hormones on new AEDs are most relevant with respect to the menstrual cycle and pregnancy. These issues are discussed in separate sections below.

There are only very few studies on how new AEDs may exert effects on endogenous female sex hormones. Oxcarbazepine has been reported to decrease endogenous estrogen by 50% and progesterone by 58%.[26] For lamotrigine, only small and hardly clinically relevant changes (reduced estradiol and increased progesterone) have been found.[27] Levetiracetam does not seem to induce changes in female sex hormone status in prepubertal children or adult women.[28,29] There seem to be no published human studies investigating possible effects of topiramate, gabapentin, pregabalin or any of the other new AEDs on endogenous female sex hormones.

2.2. Exogenous female sex hormones

Exogenous female sex hormones are predominantly used in hormonal contraception and in hormonal replacement therapy (HRT). These are discussed in separate sections.

2.3. Endogenous male sex hormones

Women do produce male sex hormones. The most important ones are testosterone, androstendione, and dihydroepiandrosterone (DHEA). Alterations in their production may have significant consequences, e.g. disturbed metabolism or impaired fertility.

Testosterone is metabolised to estradiol by aromatase, and it has been assumed that levetiracetam may inhibit aromatase. If this is true, patients on levetiracetam may have raised testosterone levels, accompanied by reduced estradiol levels. In fact, this has been found in an in vitro study.[30] However, the only available study that investigated androgen and estrogen levels in women using levetiracetam found no differences vs. untreated controls.[28]

Lamotrigine apparently does not alter testosterone levels when compared to untreated controls or valproate-treated patients.[28,31,32] However, slightly reduced androstendione (22%) and elevated DHEA (30%) levels have been reported.[28]

Oxcarbazepine reduces testosterone levels by 25%, while DHEA and androstendione levels go up by 30% and 20%.[26]

In conclusion, with the exception of oxcarbazepine's effects on estradiol and progesterone, the impact of new AEDs on endogenous hormones – as far as they have been studied – seems to be rather moderate.

2.4. Sex hormone binding globulin

Sex hormone binding globulin (SHBG) is a liver-derived glycoprotein that transports sex hormones and regulates their access to target tissues.[33] AED-induced changes in SHBG levels may thus be relevant for sex hormone functioning and homeostasis. Lamotrigine has been shown not to affect SHBG levels significantly,[27,28,32,34] although Hill et al.[27] and Sidhu et al.[34] found lowered values in lamotrigine-treated women vs. controls. Likewise, levetiracetam does not seem to affect SHBG levels.[28] By contrast, oxcarbazepine increases SHBG by 10–20%. This effect may contribute to the lower levels of estradiol and progesterone found with oxcarbazepine treatment.[26] No data on SHBG *in women* are available for the other new AEDs.

3. Menstrual cycle

Estradiol up-regulates the expression of uridinediphosphate-glucuronosyltransferase (UGT) 1A4.[35] This enzyme catalyzes the metabolism of lamotrigine, and also retigabine/ezogabine. As shown by Sidhu et al.[34] (discussed below), the estrogen-mediated induction of UGT1A4 vanishes within a few days after stopping the intake of ethinyl estradiol containing contraceptives, and lamotrigine serum concentrations may double within one week. Similarly, physiological serum concentrations of endogenous estradiol vary considerably during the menstrual cycle. Extrapolating the findings of Sidhu et al.[34] one might expect similar ups and downs of lamotrigine levels. However, several studies show that fluctuating serum concentrations of endogenous estradiol or progesterone during the menstrual cycle do not affect lamotrigine serum concentrations in a clinically relevant manner.[36–38] Neither retigabine/ezogabine (also a UGT-substrate) nor any of the other new AEDs have been studied in this regard. However, during the luteal phase of the menstrual cycle, renal blood flow, glomerular filtration rate and body water may increase by up to 10%.[39] As is the case with, e.g. serum sodium or serum albumin, serum concentrations of most drugs, especially those with primarily renal elimination (e.g., gabapentin, pregabalin or levetiracetam) may decline accordingly, i.e. by a magnitude of 5–10%. Such changes are so small that they have to be regarded as clinically irrelevant. Unfortunately, as mentioned above, there is a substantial lack of data supporting these considerations.

4. Hormonal contraception

4.1. Effects of new AEDs on hormonal contraception

It is well known that traditional AEDs like phenytoin or carbamazepine can reduce the effect of hormonal contraception via induction of cytochome enzymes. Thus, it has become standard procedure during the development of new AEDs to examine their possible effects on hormonal contraception. Many of the new AEDs have been tested for possible impairment of hormonal contraception (Table 1). Lamotrigine, levetiracetam, gabapentin, zonisamide, lacosamide, perampanel and retigabine do not alter the serum concentrations of ethinyl estradiol.[34,40–46] Also, with the exception of lamotrigine and perampanel, they do not affect the serum concentrations of exogenous progestogens like levonorgestrel.[34,40] The effect of the latter two AEDs on progestogen levels seems to be rather modest. However, the possibility of decreased contraceptive efficacy cannot be excluded.[47,48] Oxcarbazepine and eslicarbazepine reduce exposure to both ethinyl estradiol and progestogens considerably, making hormonal contraception unreliable.[49,50] Topiramate is a moderate enzyme inducer. It has been examined in two studies, and in neither of them did it affect the kinetics of progestogens. With respect to ethinyl estradiol, one of these studies found no effect at daily topiramate doses of 50, 100 and 200 mg. However, the other study examined daily doses of 200, 400 and 800 mg, and here the maximum ethinyl estradiol