Female Sex Hormones and Epilepsy

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Abstract
The frequency of seizures in many female epilepsy patients can be affected by their menstruation cycle: a phenomenon known as 'catamenial epilepsy'. This can be classified into three types-C1 (perimenstrual catamenial epilepsy), C2 (periovulatory catamenial epilepsy), and C3 (inadequate luteal catamenial epilepsy). Hormonal contraception can also affect the control of a seizure as well as the level of some antiepileptic medications, while some anticonvulsive agents can also reduce the efficacy of contraceptive pills. There is still limited evidence on the treatment of catamenial epilepsy, but a variety of therapeutic regimens can be tried including hormonal therapy, modification of antiepileptic medication regimen during the menstruation cycle, intermittent benzodiazepine, intermittent acetazolamide, or some investigative agents such as neuroactive steroid ganaxolone.

Keywords: female sex hormones, epilepsy, catamenial epilepsy, antiepileptic medications

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A lot of female patients with epilepsy may have some fluctuations of their seizure activities during their menstrual cycle. This phenomenon is known as 'catamenial epilepsy'. Approximately one third of all female epileptic patients during child bearing age may experience an increase in seizures, up to at least double of the usual seizure frequency, at some point during their menstrual cycle.[1] This results from different pharmacological effects of major female sex hormones. Many epileptologists consider estrogen, particularly estradiol, a 'proconvulsant', an agent that may promote seizure activity, while progesterone is regarded as an 'anticonvulsant', an agent with the tendency to reduce seizure frequency.[2] Such theories are supported by several animal studies. For example, estradiol can induce new cortical seizure foci when applied topically, or reduce the seizure threshold in the maximal electroshock seizure models, whereas progesterone leads to the opposite effect.[3] Therefore any variation in the relative levels of estrogen and progesterone can significantly affect seizure frequency over the course of a menstrual cycle.

Menstrual Cycle

A normal menstrual cycle (Figure 1) results from the secretion of follicular stimulating hormone (FSH) by the anterior pituitary gland. The rise in FSH level stimulates the growth of ovarian follicles (**'follicular phase'** of the ovarian cycle). The secretion of estrogen through the growing ovarian follicles is responsible for the proliferation of the endometrium (**'proliferative phase'** of the uterine cycle). When the follicle is sufficient for ovulation (Graafian follicle), there is a surge of the level of luteinizing hormone (LH), resulting in **ovulation**. After ovulation, FSH and LH cause the remaining part of the dominant follicle to transform into the corpus luteum, and the ovary turns into the **'luteal phase'**. The corpus luteum is responsible for a production of large amounts of progesterone. Under the influence of progesterone, the endometrium changes to prepare for potential conception of an embryo

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Received: June, 26, 2015.
Revision received: July, 1, 2015.
Accepted after revision: July, 1, 2015.
Bangkok Med J 2015;10:65-71.
E-journal: http://www.bangkokmedjournal.com

Dear readers

This is our 10th anniversary edition of the Bangkok Medical Journal, where we share the very latest technological innovations and discoveries in special features, original articles, case studies and reviews.

We are deeply privileged to share a Special Feature from Anekpuritanang T, Rameshwar Patil and Keith L. Black, MD reporting on the extraordinary breakthroughs that are taking place in the field of advanced imaging. We would like to extend our most sincere thanks to all concerned for this article, and the opportunity to share this pioneering work with our readers. Professor Black and colleagues have been working to improve the quality and sensitivity of imaging in the early detection of conditions from brain tumors to Alzheimer's disease to enhance treatment protocols and patient management. The team introduced nanoparticles to improve MRI imaging and this is proving to be very efficient, highly successful and extremely encouraging for the future clinical outcomes for patients.

Anekpuritanang T, MD presents on the DISH technique as a diagnostic tool for *HER2*. *HER2* is an epidermal growth factor receptor-2. In recent years, *HER2* has played an important role in diagnosis and therapeutic management of various cancers including: glioblastoma, breast cancer, lung cancer, gastric, ovarian and endometrial cancers. This has several advantages: it is inexpensive, easy to identify and can be archived for re-examination. The efficiency is equal to the gold standard FISH technique.

In the therapeutic field, Rameshwar Patil, MD, Keith L. Black, MD and colleagues have been able to conjugate a polymelic acid platform with monoclonal antibodies (mAbs) and Gd–DOTA, called nanoimaging agents (NIA). These can penetrate the endothelial blood brain barrier (BBB). Furthermore, mAbs can penetrate brain tissue or other organs which in turn will lead to better treatment and clinical outcomes. This pioneering work by Professor Black, and colleagues, gives rise to a new hope for cancer patients for targeted therapy and for immunotherapies in Alzheimer's disease.

Dr. Gumpanart Veerakul reports on a coronary slow flow (CSF) phenomenon case, where the angiography and intracoronary ultrasound imaging showed no significant plaque burden. Although CSF was identified 43 years ago, its pathogenic mechanisms remain unknown. This case raises awareness of the importance of controlling all coronary risk factors to prevent the potentially lethal CSF phenomenon.

The practice of transporting patients with extracorporeal membrane oxygenator (ECMO) is very new to Thailand and Bangkok Hospital has been offering this service since 2014, with good results. Dr Sakiyalak reports on several cases from referral hospitals to Bangkok Hospital and the inherent challenges.

Dr. Chaothawee reports on the atrial myxoma as a learning model to assess cardiac tumors using MRI. The atrial myxoma is a commonly occurring primary benign cardiac tumor with very particular distinguishing characteristics. We also report on cases of isolated liver metastases, primary renal synovial sarcoma and lung carcinoid tumor, successfully treated with bronchoscopic cryosurgery.

We trust you will find informative and innovative discussions in this edition of the Bangkok Medical Journal. We remain true to our pledge to encourage practitioners to continue medical education.

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ISSN 2287-0237 (online)/ 2287-9674 (print)

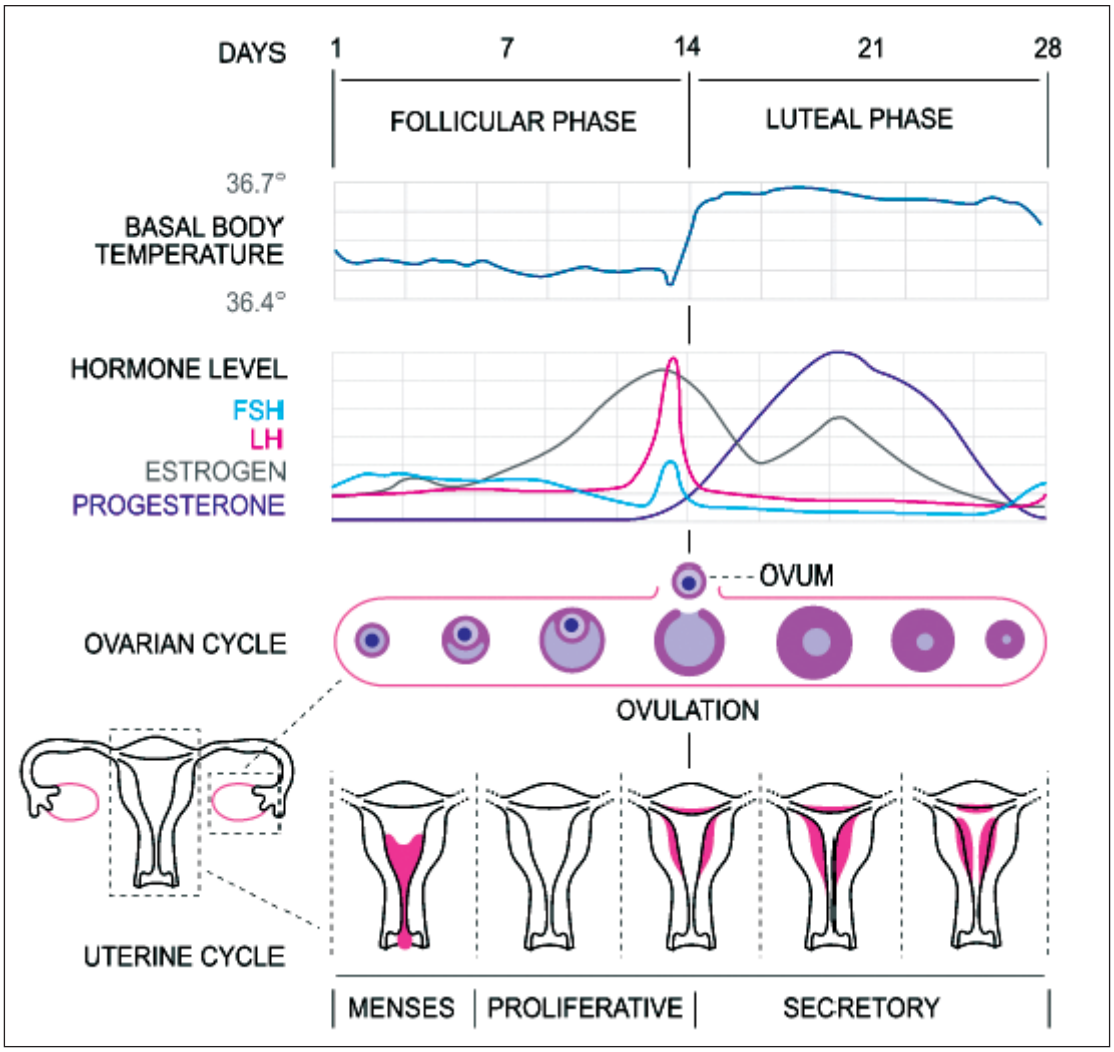

Figure 1: Normal menstrual cycle.[5]

(**'secretory phase'** of the uterine cycle). If pregnancy does not occur, the corpus luteum will involute, causing sharp drops in blood levels of both estrogen and progesterone. The drop of the hormone levels signals the body to start shredding the inner lining of uterus, resulting in **menstruation** (**'progesterone withdrawal bleeding'**).[4]

In some patients with chronic stress, insufficient dietary intake, excessive exercise, or abnormal hormone levels in the blood stream, the ovaries may not undergo ovulation. Therefore, the progesterone levels remain low at all times. Such a menstrual cycle is termed **'anovulatory cycle'**. These patients may experience periodic vagina bleeding similar to menstruation that results from the inability of growing ovaries to secrete enough estrogen to maintain the proliferation of the endometrium (**'estrogen breakthrough bleeding'**).[4]

Catamenial Epilepsy

According to the study by Herzog and colleagues in 1997,[6] catamenial epilepsy can be classified into three types as follow (Figure 2A and 2B):

1. Perimenstrual catamenial epilepsy or Catamenial 1 (C1)
2. Periovulatory catamenial epilepsy or Catamenial 2 (C2)
3. Inadequate luteal catamenial epilepsy or Catamenial 3 (C3)

C1 and C2 catamenial epilepsy is seen in women with a normal menstrual cycle due to an increased estrogen to progesterone ratio during the perimenstrual and periovulatory periods. A C3 pattern occurs in patients with an anovulatory cycle, presenting always with abnormally low progesterone levels. These patients tend to have seizures when there is a rise in estrogen especially in the latter half of the menstrual cycle.

ISSN 2287-0237 (online)/ 2287-9674 (print)

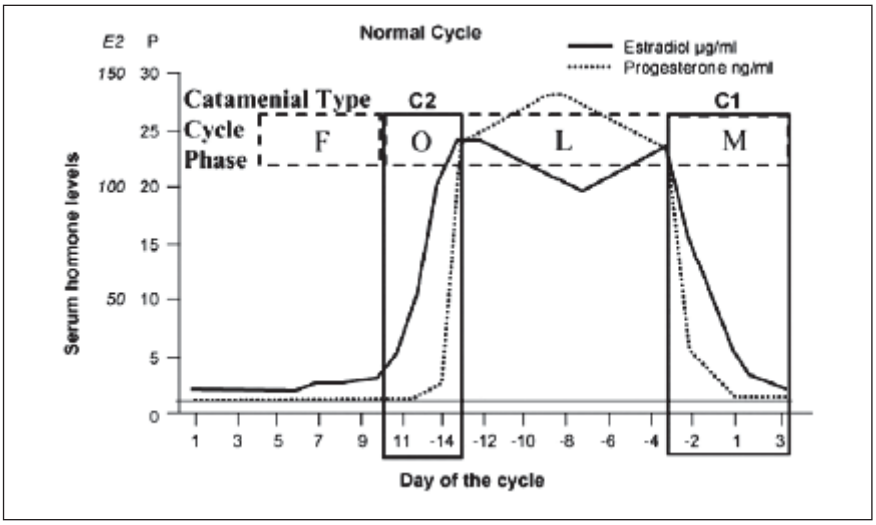

Figure 2A: Catamenial epilepsy associated with normal menstrual cycle.[7]

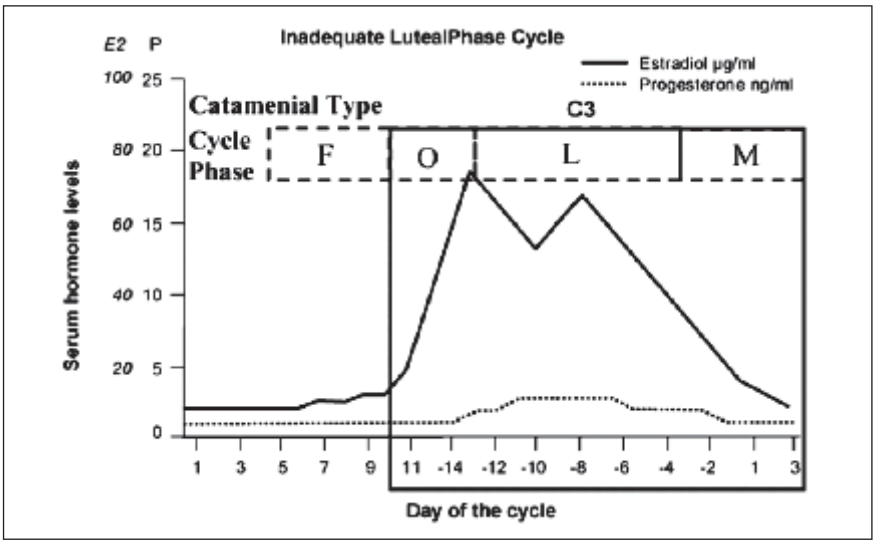

Figure 2B: Catamenial epilepsy associated with normal menstrual cycle.[7]

Hormonal Contraception and Epilepsy

Hormonal Contraception is another factor that may affect the frequency of seizures in epileptic patients. There are two main types of hormonal contraception as follows.[8]

1. Combination Methods

The combination methods are birth control strategies that utilize both estrogen and progesterone. The purpose of estrogen use is to prevent the rise of FSH so that follicles cannot fully develop, while progesterone works by inhibiting the LH surge resulting in suppression of ovulation. In addition, progesterone changes the characteristic of cervical mucus for it to become thicker and more viscous, inhibiting the passing of sperms through the cervix for fertilization. Combination methods are mostly achieved by the use of combined oral contraceptive pills, but some patients may opt for combined injectable contraception.

The combination methods are considered as a highly effective contraceptive strategy. The pregnancy rate is less than 1% when the patients take the prescribed medicine regularly. Since a higher dose of estrogen may result in some adverse effects such as nausea, vomiting, migraine and dizziness, modern combined contraceptive pills usually contain reduced amount of estrogen, i.e., less than 50 micrograms of ethinyl estradiol. However, some women with low estrogen levels at baseline may be affected by intermittent vaginal bleeding similar to the beginning of their menstruation or, in some cases, even miss their periods. In such patients, contraceptive pills with a higher dose of estrogen may be necessary.

As the estrogen hormone is considered proconvulsant, epileptic patients should avoid using combination methods for contraception, or opt for using the lowest amount of estrogen as possible. A summary of combined oral contraceptive options is provided in Table 1.

ISSN 2287-0237 (online)/ 2287-9674 (print)

Table 1: A summary of combined oral contraceptive options.

Types of oral contraceptive pills	Hormone Content	
	Estrogen	Progestogen
Anna	ethinyl estradiol 30 µg	levonorgestrel 0.15 mg
Annylyn	ethinyl estradiol 20 µg	gestodene 75 µg
Daisy	ethinyl estradiol 30 µg	desogestrel 0.15 mg
Diane	ethinyl estradiol 35 µg	cyproterone acetate 2 mg
Dior	ethinyl estradiol 30 µg	D-norgestrel 0.15 mg
Lindynette	ethinyl estradiol 20 µg	gestodene 75 µg
Marvelon	ethinyl estradiol 30 µg	desogestrel 0.15 mg
Meliane	ethinyl estradiol 20 µg	gestodene 75 µg
Melodia	ethinyl estradiol 30 µg	drospirenone 3 mg
Mercilon	ethinyl estradiol 20 µg	desogestrel 0.15 mg
Microgynon	ethinyl estradiol 30 µg	levonorgestrel 0.15 mg
Minidoz	ethinyl estradiol 15 µg	gestodene 60 µg
Oilezz	ethinyl estradiol 20 µg	desogestrel 0.15 mg
Sucee	ethinyl estradiol 35 µg	cyproterone acetate 2 mg
Synfonia	ethinyl estradiol 20 µg	drospirenone 3 mg
Yasmin	ethinyl estradiol 30 µg	drospirenone 3 mg
YAZ	ethinyl estradiol 20 µg	drospirenone 3 mg

2. Progestogen-only methods

This contraception method relies on the use of constant progesterone level in order to suppress ovulation, with the aim of preventing the adverse effects of estrogen. The efficacy of this regimen is approximately 92-99% which is slightly lower than the combination methods. The major adverse effect of progestogen-only method includes unpredictable breakthrough bleeding.

Progestogen-only contraceptive methods can be achieved by several means including oral birth control pills (minipills), contraceptive injection (e.g., Depo-Provera), or contraceptive implants (e.g., Implanon).

The Effects of Female Sex Hormones on Antiepileptic Drugs (AEDs)

In addition to the frequency of seizures, female sex hormones may affect the levels of some antiepileptic medications, particularly those undergoing cytochrome P450 metabolism in the liver such as lamotrigine.

Lamotrigine is primarily (approximately 90%) metabolized by glucuronidation using the enzyme UDP glucuronosyltransferase 1A4 (UGT1A4) in the liver.[9] Estrogen increases the clearance of lamotrigine by inducing the liver enzymes involved in its metabolism. More rapid metabolism results in lower levels of lamotrigine. Several studies carried out in female epileptic patients revealed that hormonal contraceptives may alter the blood levels and efficacy of lamotrigine, decreasing its concentration by as much as 50%.[10] The efficacy of birth control pills in women who take combination pills is significantly more affected than that of the women taking progestogen-only pills, indicating that estrogen strongly affects the efficacy of lamotrigine while progesterone does not.[11]

Contraceptive pills may also affect the glucuronidation process of other anticonvulsants resulting in altered blood levels and efficacy. For example, the level of valproic acid can be reduced by 23% in women taking combination pills[12] (approximately 30-50% of valproic acid metabolism requires glucuronidation).

In pregnant women, the levels of estrogen and progesterone may rise significantly, therefore affecting the levels of several antiepileptic medications including lamotrigine (Figure 3)[13], valproic acid, and oxcarbazepine. This results from estrogen inducing the glucuronidation metabolism as described above. Thus, in well-controlled epileptic patients who plan to become pregnant, physicians should obtain the drug level at baseline so that the dose of antiepileptic medications can be calculated and adjusted appropriately as the pregnancy progresses. The dose of lamotrigine may need to be increased by two to three-fold in the last semester of pregnancy.

ISSN 2287-0237 (online)/ 2287-9674 (print)

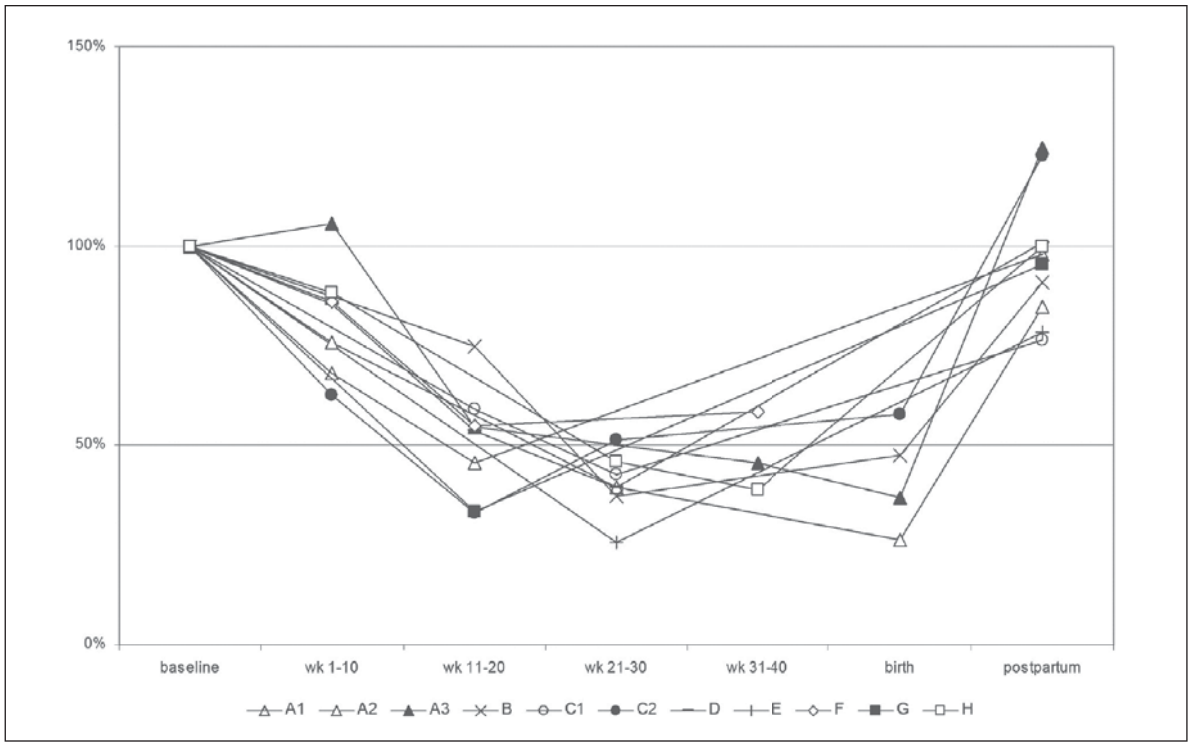

Figure 3: The blood concentration of lamotrigine in each gestational period.[13]

Table 2: List of anti-Epileptic medications that affect the efficacy of oral contraceptives.

AEDs that decrease the effectiveness of oral contraceptives	AEDs that may decrease the effectiveness of oral contraceptives	AEDs that do not decrease the effectiveness of oral contraceptives
carbamazepine	lamotrigine	clobazam
oxcarbazepine		clonazepam
perampanel		ethosuximide
phenobarbital		gabapentin
phenytoin		lacosamide
primidone		levetiracetam
rufinamide		pregabalin
topiramate		tiagabine
		valproic acid
		vigabatrin
		zonisamide

The Effects of Antiepileptic Drugs (AEDs) on Female Sex Hormones

Several antiepileptic medications are hepatic enzyme inducers, therefore promoting the elimination of other drugs requiring liver metabolism. Since estrogen also undergoes glucuronidation in the liver, its level can be affected by enzyme inducers. As a result, some anticonvulsive agents may affect the efficacy of oral contraceptives, thus, increasing the risk of unplanned pregnancy.[14] The effects of antiepileptic drugs on female sex hormones are summarized in Table 2.

For the female epileptic patients who take both enzyme inducing antiepileptic medications and oral contraceptive pills, physicians should also recommend other non-hormonal contraceptive methods, such as intrauterine devices, barrier methods such as male and female condoms, vaginal diaphragm, or cervical cap.

ISSN 2287-0237 (online)/ 2287-9674 (print)

Treatment of Catamenial Epilepsy

There remains limited evidence regarding the treatment of catamenial epilepsy. Most of the studies are anecdotal reports or small open-label trials. A variety of therapeutic regimens can be tried as follow:

1. Hormonal Therapy

The principle of this treatment is that progesterone has some anticonvulsive activity. For that reason, progesterone may be used in the latter half of the menstrual cycle. Initial small clinical trials suggest that cyclical progesterone therapy may be beneficial in some catamenial epilepsy patients.[15-17] However, the most recent randomized, double-blinded, placebo-controlled, multicenter clinical trial by Herzog and colleagues in 2012 revealed that this method does not significantly reduce the frequency of catamenial seizures.[18]

2. Modification of Antiepileptic Medication Regimen

Although this method is used by several physicians, there has been no systematic study on the modification of antiepileptic medication regimen for the treatment of catamenial epilepsy.[7] The dose of antiepileptic medication can be increased slightly during the part of the menstruation cycle with higher potential for seizures. To be able to achieve this regimen, patients must be compliant and well informed about the antiepileptic medication schedule. In addition, this method is only useful for women with regular menstruation cycles who have not yet achieved the maximum dose of antiepileptic medication (as there is still some room to increase the dose of an antiepileptic agent). This regimen can be used with medications of linear pharmacokinetics, i.e., physicians can predict the blood level of medications according to the dose increase. Therefore, a commonly prescribed antiepileptic drug, such as phenytoin (zero-order pharmacokinetics), is not appropriate for this regimen.

3. Intermittent Benzodiazepines

This treatment method is to intermittently use benzodiazepines such as clobazam or lorazepam during the period of high potential for seizures in order to prevent drug tolerance should the medicine be used continuously. The double-blinded crossover study conducted by Feely et al. in 1982 reported that the use of clobazam 20-30 mg/day for 10 days with the highest potential for seizure exacerbation could prevent seizures in 14 patients of the 18 patients enrolled in this study.[19]

4. Intermittent Acetazolamide

Several small studies reported that the use of acetazolamide, 250-1000 mg per day (divided twice daily) for 3-7 days prior to menstruation can prevent catamenial epilepsy.[20] Although the mechanism of action remains unclear, it is believed that acetazolamide prevents the seizures by its carbonic anhydrase inhibitor property.

5. Neuroactive Steroid

Ganaxolone is a neuroactive steroid with a structure similar to progesterone. It possesses a positive allosteroic modulatory effect at the neurosteroid binding site on the GABAA receptor complex. It has beneficial activity in a broad range of animal models of epilepsy. Ganaxolone also has the advantage that it lacks female hormonal activity, and thus can be applied across both genders and all ages. According to preliminary studies, ganaxolone may be effective for patients with catamenial epilepsy.[21] It is currently undergoing a phase III clinical study which is expected to be completed by mid-2015.

Conclusion

There are several considerations with regards to the treatment of women with epilepsy, since the interactions between female sex hormones, seizure susceptibility and antiepileptic medications are complex. A mastery of basic physiology, as well as an in-depth understanding of pharmacokinetics of both hormones and anticonvulsive agents, is crucial for developing strategies to improve seizure control in catamenial epilepsy patients.

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ISSN 2287-0237 (online)/ 2287-9674 (print)

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