Curr Treat Options Neurol (2014) 16:288
DOI 10.1007/s11940-014-0288-3

EPILEPSY (E WATERHOUSE, SECTION EDITOR)

Anti-Epileptic Drugs and Hormonal Treatments

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Published online: 1 April 2014

This article is part of the Topical Collection on *Epilepsy*

Keywords Epilepsy · Anti-epileptic drugs · Phenobarbitone · Phenytoin · Sodium valproate · Lamotrigine · Carbamazepine · Oxcarbazepine · Eslicarbazepine · Gabapentin · Pregabalin · Tiagabine · Topiramate · Zonisamide · Benzodiazepines · Ethosuximide · Perampanel · Hormones · Contraception · Oral contraceptive pill · Medroxyprogesterone · Norethisterone · Levonorgestrel implants · Intra-uterine contraceptive device · Contraceptive implant

Opinion statement

Epilepsy and the medications used in its treatment are known to affect the menstrual cycle, aspects of contraception, and bone health in women. Adolescence is an important time to review the diagnosis of both epilepsy and the epilepsy syndrome because of the implications and decisions, which should be made regarding antiepileptic drug (AED) treatment. In girls, once they are on AED therapy, seizure free, and driving, it becomes difficult to change therapy because of the risk of breakthrough seizures and the fact that the new AED may not be as effective as the first. So a treatment choice made in adolescence is often life-long. Therefore, women need to be started on an AED that currently appears to be the most suitable for their seizure type, has a low teratogenic risk, and hopefully does not interact with contraception. There are no contraindications to the use of non-hormonal methods of contraception in women with epilepsy. Nonenzyme-inducing AEDs (valproate, benzodiazepines, ethosuximide, levetiracetam, tiagabine, and zonisamide) do not show any interactions with the combined oral contraceptive. There are interactions between the combined oral contraceptive and hepatic microsomal-inducing AEDs (phenytoin, barbiturates, carbamazepine, topiramate [dosages >200 mg/day], oxcarbazepine, eslicarbazepine and perampanel [dosages >12 mg/day]) and lamotrigine. Women taking enzyme inducing AEDs should be encouraged to use a method of contraception that is unaffected by their epilepsy medication. Interactions between AEDs and other hormonal therapies are less well studied. Studies have suggested that women with epilepsy are at increased risk of fractures, osteoporosis, and osteomalacia. No studies have been undertaken looking at preventative therapies for these comorbidities. This article will concentrate on current contraceptive treatment options in patients taking AEDs.

Introduction

Hormonal contraceptives include some of the most effective options when deciding upon birth control measures [1, Class II]. They work by inhibiting ovulation and fertilization and take the form of oral contraceptive pills, topical patches, intramuscular depot injections, implants and intrauterine devices. When patients with epilepsy are choosing contraception there are important considerations to take into account. There are complex interactions between anti-epileptic drugs (AEDs) and hormonal therapies and for hormonal contraceptives this has been intensively investigated. Consequently, contraceptive advice needs to be individualised for patients with epilepsy according to the combination of AEDs taken to avoid contraceptive failure and to prevent detrimental effects of the hormonal therapy on the effectiveness of the AEDs.

Contraceptive failure with AED occurs by hepatic P450 microsomal enzyme induction. Many of the older generation of AEDs cause enzyme induction (barbiturates, phenytoin, and carbamazepine), whereas some of the newer AEDs tend not to. Anti-epileptic drugs such as lamotrigine, levetiracetam, gabapentin, pregabalin, vigabatrin, tiagabine, zonisamide, and lacosamide do not alter testosterone or estrogen levels in women [2••, Class IV]. Oxcarbazepine and eslicarbazepine are exceptions as they are inducers of the cytochrome P450 enzymes [3, 4••, Class IV]. There is evidence that topiramate and perampanel are less potent inducers and may interact with the oral contraceptive (OC) in a dose-dependent manner [5••, Class IV].

Oral contraceptive medications may also, potentially, have an effect on the AEDs. The combined oral contraceptive pill (COCP) can alter the efficacy of certain AEDs, by increasing the metabolism of glucuronidated drugs, through induction of the uridine-diphosphate glucuronosyltransferase system (UGT1A4). This has been most intensively studied for lamotrigine and is most likely secondary to increased drug glucuronidation [6, 7, Class I]. The change in lamotrigine metabolism is attributed to the estrogen rather than the progestin component of the COCP [8, Class I].The plasma level of lamotrigine increases rapidly by 25 %–50 % in the "pill-free" week [7]. The level of altered elimination induced by the COCP is unpredictable in an individual patient [9, Class III]. Recent results suggest that valproate, which is eliminated mainly by glucuronidation, may have a similar but less pronounced interaction with the COCP [10, Class II]. Also, theoretically the pharmacologically active monohydroxy derivate (MHD) of oxcarbazepine may be affected by the COCP, but this possible interaction needs to be further explored.

Treatment

Oral contraceptive drugs

- The dose of oral contraceptive medication may need to be altered when used in combination with some AEDs to provide effective contraceptive levels. Treatment with phenytoin, phenobarbital, primidone and carbamazepine, and the COCP results in a significant reduction in the amount of the contraceptive steroids. Medications that induce the hepatic CYP3A4 isoenzyme accelerate the hydroxylation of estrogen to inactive metabolites. This can result in decreased serum concentrations of the OC resulting in contraceptive failure. With phenytoin, carbamazepine, and phenobarbital, there is dose-dependent enzyme induction [11, Class I; 12, Class II], although the extent of enzyme induction in an individual patient is unpredictable because genetic and environmental factors as well as concurrent disease influence hepatic isoenzyme expression [13–16, Class IV].
- A recent double-blind, randomized, placebo-controlled crossover study of 10 women given carbamazepine with a low-dose COCP (20 mcg ethinylestradiol and 100 mcg levonorgestrel) showed sig-

nificantly lower mean area under the curve measurements. Higher rates of ovulation and breakthrough bleeding were also seen with carbamazepine, although this was not statistically significant likely because of the small sample size [17, Class II]. Although not formally studied, higher dose OCs are likely to maintain adequate levels of contraceptive hormones.

- The newer AEDs oxcarbazepine and eslicarbazepine are also considered to be inducers of cytochrome P450 enzymes [5••].
- Levetiracetam, gabapentin, pregabalin [18–20, Class II], vigabatrin [21, Class I], tiagabine, zonisamide [22–24, Class II], and lacosamide [25, Class I] have no known interactions with the OC.
- There were no significant differences in the kinetics of ethinylestradiol and levonorgestrel before and during treatment with sodium valproate [26–29, Class II]. Therefore, the OC remains effective at standard doses in combination with sodium valproate.
- The 12 mg dose of perampanel in patients on the combined OC resulted in a reduction in levonorgestrel exposure. The mean peak serum concentration (Cmax) and area under the curve (AUC) values where both reduced by 40 % according to the summary of product characteristics (SPC). Lower doses (4 and 8 mg) were unaffected. In women using 12 mg/day, there is a possibility of reduced efficacy in women using progestogen containing oral contraceptives. An alternative (progestogen-only injectable or intrauterine) or additional reliable method (intra-uterine device or condom) should be used [5••].
- Women taking phenytoin, phenobarbital, or carbamazepine need to take a combination of oral contraceptive pills with at least 50 μg of estrogen (an off license use) [30]. There are no suitable 50 μg preparations licensed in the UK or the US. An alternative suggestion is the use of emergency contraception taken regularly [2••].
- The usual 7-day pill-free interval may weaken the contraceptive effect, so the pill should be given in a tricycling regimen (three cycles of COCPs consecutively without a break) followed by a shorter pill-free interval of 4 days [31, Class IV]. Breakthrough bleeding usually settles during the first two to three cycles; if not, contraception failure is possible and the dose of estrogen may need to be increased, but should not exceed 100 mcg per day [32, 33•, Class IV].
- There is no interaction data available for the progesterone only pill (POP), but this method of contraception is likely to be unreliable in women on enzyme-inducing anti-epileptic drugs. Desogestrel inhibits ovulation with a peak blood level about six times the ovulatory inhibitory level and theoretically might be effective in a twice daily dosage in combination with enzyme inducing AEDs but no data exists [32, Class VI].

Combined oral contraceptive pill

Standard dosage (UK) Varies according to brand. Multiple brands available. Most contain 30–35 mcg ethinylestradiol. A newer estradiol containing COCP is available. The progesterone component varies according to brand.

Contraindications	Migraine with aura, past venous or arterial thrombosis, severe or multiple risk factors for arterial disease or venous thromboembolism including systemic lupus erythematosis with positive antiphospholipid antibodies, gall stones, history of breast cancer. Avoid in active liver disease.
Main drug interactions	Effectiveness reduced by enzyme inducing medications taken concurrently or within the last 28 days.
Main side effects	Nausea and vomiting, abdominal cramps, weight changes, liver impairment, headache, mood changes, changes in libido.
Special points	Extra precautions needed with missed pills or diarrhea and vomiting.
Cost	Low.

Progesterone only pill

Standard dosage (UK)	Desogestrel 75 micrograms (Cerazette), norethisterone 350 micrograms (Micronor or Noriday), etynodioldiacetate 500 micrograms (Femulen), and levonorgestrel 30 micrograms (Norgeston).
Contraindications	Undiagnosed vaginal bleeding, severe arterial disease, breast cancer, or acute porphyria.
Main drug interactions	Effectiveness reduced by enzyme inducing drugs.
Main side effects	Menstrual irregularities, nausea, vomiting, headache, dizziness, breast discomfort, and weight changes.
Special points	Extra precautions needed with missed pills or diarrhea and vomiting.
Cost	Low.

Intramuscular injections

- There is no evidence as to whether hepatic microsomal enzyme inducing AEDs reduce the efficacy of medroxyprogesterone (Depo-Provera) or norethisterone (Noristerat) injections but theoretically they might. In the past, many neurologists have recommended that the frequency of injection for women taking such drugs be increased (eg, to every 10 weeks from the usual 12 for Depo-Provera), although there is no evidence that this should be done [34, 35, Class IV]. The rate limiting step in the metabolism of depot medroxyprogesterone acetate is hepatic blood flow, and in theory, this makes enzyme induction irrelevant [33•, 36, Class VI]. In adolescent girls, there is some evidence to suggest that Depo-Provera may interfere with the achievement of peak bone mass [37, Class II], a problem also encountered with AEDs such as carbamazepine, phenytoin, barbiturates, and valproate.

Medroxyprogesterone acetate (Depo-Provera)

Standard dosage	150 mg intramuscularly every 12 weeks.
Contraindications	Undiagnosed vaginal bleeding, severe arterial disease, breast cancer, or acute porphyria.
Main drug interactions	Effectiveness not known to be reduced by enzyme inducing medications but theoretically might consider shortening interval between injections from 12 to 10 weeks.

Main side effects	Menstrual irregularities, nausea, vomiting, headache, dizziness, breast discomfort, and weight changes.
Special points	None.
Cost	Low.

Norethisterone enantate

Standard dosage	200 mg every 8 weeks.
Contraindications	Undiagnosed vaginal bleeding, severe arterial disease, breast cancer, or acute porphyria.
Main drug interactions	Effectiveness not known to be reduced by enzyme inducing medications but theoretically might consider shortening interval between injections.
Main side effects	Menstrual irregularities, nausea, vomiting, headache, dizziness, breast discomfort, and weight changes.
Special points	None.
Cost	Low.

Implants

- There have been more than 30 contraceptive failures among women with epilepsy reported to the manufacturers with levonorgestrel implants. Norplant subdermal capsules were implanted into nine women with epilepsy and 10 controls. Eight of the nine women were on enzyme inducing anti-epileptic drugs (two-phenytoin monotherapy, three-phenytoin and carbamazepine, two-carbamazepine monotherapy, one-phenytoin and sodium valproate). At 3 to 6 months, the mean overall plasma levonorgestrel concentration was significantly lower in the six women with epilepsy who were taking phenytoin (203+128 pg/mL) than in the controls (325+135 pg/mL, $P<0.01$). After 1 year, nine of the 10 control women continued to use Norplant and no pregnancies had occurred. Two of the nine women with epilepsy had become pregnant during contraception with Norplant. They were both on phenytoin, and their plasma concentrations of levonorgestrel were low at the time of conception. Levonorgestrel released from the capsules did not alter seizure frequency [38, Class II]. Contraceptive failure has also been reported with Implanon [39, Class III]. In conclusion, implantable progestogen contraceptives should not be used as a method of contraception by women on enzyme-inducing anti-epileptic drugs.

Emergency contraception

- The progestogen-only emergency contraceptive can be taken up to 72 hours after unprotected intercourse, and prevents more than 90 % of pregnancies if taken within 24 hours. The copper intra-uterine

contraceptive device (IUCD) can be used as emergency contraception within 5 days of having unprotected sexual intercourse and has a success rate approaching 100 %. Women should be informed about lack of data on the efficacy of the progestogen-only emergency contraceptive pill when using enzyme inducing AEDs and should be offered an IUD as an alternative. Women taking enzyme inducing AEDs who require progestogen-only emergency contraception should use twice the normal dose of Levonorgestrel [32]. The summary of product characteristics (SPC) for ulipristal acetate states that it should not be used in patients taking enzyme-inducing medications [40, Class IV].

Levonorgestrel (Levonelle-1500 or Levonelle-One Step)

Standard dosage	1.5 mg single dose after unprotected sexual intercourse or contraceptive failure, taken as soon as possible and licensed for up to 72 hours.
Contraindications	Acute porphyria
Main drug interactions	Effectiveness may be reduced by enzyme inducing medications.
Main side effects	Menstrual irregularities, nausea, lower abdominal pain, fatigue, headache, dizziness, mastalgia, and vomiting.
Special points	For patients taking enzyme-inducing medications, this is considered second line emergency contraceptive after the copper IUCD. The dose should be doubled in women taking or who have taken enzyme inducing AEDs within the last 28 days (outside product license, Faculty for Sexual and Reproductive Healthcare 2010).
Cost	Low.

Ulipristal acetate (EllaOne)

Standard dosage	30 mg single dose as soon as possible after coitus but no later than 120 hours.
Contraindications	Severe asthma insufficiently controlled by oral glucocorticoid.
Main drug interactions	Effectiveness may be reduced by enzyme inducing medications. The SPC states that it is not advisable to use ulipristal acetate with enzyme-inducing medications.
Main side effects	Gastrointestinal disturbances, dizziness, fatigue, headache, menstrual irregularities, back pain, muscle spasms. Less commonly hot flushes, uterine spasm, breast tenderness.
Special points	Not for use in women taking enzyme inducing AEDs according to the SPC. A repeat dose should be taken if vomiting occurs within 3 hours of administration. May reduce the contraceptive action of regular hormonal contraception, and it is recommended that reliable barrier contraception is used until the next menstrual period starts. Breast feeding is not recommended for 36 hours after administration.
Cost	Low.

Interventional procedures

	• Intrauterine devices or systems are small, often T-shaped devices that are fitted into the uterus. They contain either copper (Paragard) or Levonorgestrel (Mirena or Skyla). Contraceptive effects for the latter type are mainly local and not affected by the presence or absence of enzyme inducing anti-epileptic drugs [41, Class III]. Therefore, this remains an effective method of contraception for women with epilepsy.
Contraindications	Pregnancy, undiagnosed abnormal genital bleeding, current genital infection, pelvic inflammatory disease, postpartum endometritis, infected abortion in the last 3 months, cervical or uterine malignancies, cervical dysplasia, previous or active severe arterial disease, liver disease, or past bacterial endocarditis/severe pelvic infection in a women with a prosthetic heart valve or anatomical heart defect.
Complications	Pain, expulsion, uterine perforation, pelvic inflammatory disease, irregular menses, ovarian cysts, and ectopic pregnancy.
Special points	Pain is more likely to occur in nulliparous women.
Cost	Low.

Compliance with Ethics Guidelines

Conflict of Interest

Clare A. Johnston has had travel/accommodations expenses covered/reimbursed by Pfizer. Pamela M. Crawford has had travel/accommodations expenses covered/reimbursed by UCB and Eisai.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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