

Contraception for women taking antiepileptic drugs

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Abstract

Antiepileptic drugs (AEDs) that induce hepatic enzyme activity may alter the metabolism of most hormonal methods of contraception, and this may affect their contraceptive efficacy. There is also the potential for the hormonal method to affect the AED. Women may also be prescribed AEDs to treat conditions other than epilepsy, such as chronic pain and migraine. These effects should be considered in the choice of both the treatment of the

epilepsy and the choice of contraceptive method. This review considers these interactions and offers advice about their management.

Keywords antiepileptic drugs, contraception, epilepsy, liver enzyme induction, women

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Introduction

Epilepsy affects up to 1.0% of the population. About half of these patients are women, many of childbearing age, and most of them will seek advice about contraception at some time. The choice of contraceptive method is influenced by many factors, and women will expect, and should receive, appropriate information about the various options for safe and effective contraception.¹ This counselling requires a consideration of the age of the patient, their socioeconomic and educational status, the type of epilepsy and the most suitable antiepileptic drug (AED) treatment. This short review summarises those factors specific to epilepsy that influence this choice and makes recommendations about contraceptive practice for these patients. This information also applies to women prescribed AEDs for the treatment of chronic pain conditions and migraine. In general, women on AEDs may use a hormonal contraceptive if they wish to do so, after a full discussion with their physician of the alternatives available and any recommended modifications of the chosen regimen that may be necessary.

The optimal choice of hormonal contraceptive is affected by whether or not the prescribed antiepileptic medication induces liver enzyme activity [i.e. an enzyme-inducing antiepileptic drug (EIAED)].

Important Note: Some of the practical management suggestions in this review are not licensed and if used they should be prescribed on a 'named patient basis'² by a registered medical practitioner. These recommendations are indicated in the text by the abbreviation NL.

Interaction of hormonal contraceptives with AEDs

Some AEDs induce cytochrome P450 hepatic enzyme activity, which increases the rate of metabolism of both ethinylestradiol (EE) and progestogens, thereby lowering the blood levels of these hormones, perhaps by 50% or more (Tables 1 and 2), dependent on individual variation.

It is therefore very important to know whether a patient is taking an AED that affects hormonal contraception (i.e. an EIAED) before prescribing a hormonal contraceptive,

Table 1 Antiepileptic drugs (AEDs) that may reduce blood levels of contraceptive hormones

Carbamazepine (Tegretol®)
Felbamate (Felbatol®) – not available in the UK
Lamotrigine (Lamictal®) – reduces progestogen only (see below)
Oxcarbazepine (Trileptal®)
Phenobarbital
Phenytoin (Epanutin®)
Primidone (Mysoline®)
Rufinamide (Inovelon®)
Topiramate (Topamax®) – reduces the level of ethinylestradiol by about 30%, but has a negligible effect below 200 mg/day ³

Table 2 Antiepileptic drugs (AEDs) that do not affect hormonal contraception

Acetazolamide (Diamox®)
Benzodiazepines: clobazam, clonazepam (Rivotril®)
Ethosuccimide (Zarontin®)
Gabapentin (Neurontin®)
Lacosamide (Vimpat®)
Levetiracetam (Keppra®)
Pregabalin (Lyrica®)
Sodium valproate (Epilim®)
Tiagabine (Gabitril®)
Vigabatrin (Sabril®)
Zonisamide (Zonegran®)

Table 3 Methods of contraception that are affected by enzyme-inducing antiepileptic drugs (EIAEDs)

Combined oral contraceptive pill
Combined contraceptive patch (Evra®)
Combined contraceptive vaginal ring (NuvaRing®)
Progestogen-only pill
Progestogen implant (Implanon®)
Postcoital contraception (Levonelle One Step®, Levonelle 1500®, ellaOne®)

Table 4 Methods of contraception that are not affected by enzyme-inducing antiepileptic drugs (EIAEDs)

Medroxyprogesterone acetate depot injection (Depo-Provera®)
Levonorgestrel-releasing intrauterine system (Mirena®)
Other intrauterine contraceptive devices, all copper-containing
Barrier methods

and to give appropriate advice when prescribing an EIAED to women already using hormonal contraception (Tables 3 and 4).

Some AEDs are affected by hormonal contraception, and sodium valproate causes liver enzyme inhibition (Table 5).

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Table 5 Antiepileptic drugs (AEDs) affected by hormonal contraception and/or that cause liver enzyme inhibition**AEDs affected by hormonal contraception:**

Lamotrigine – see below

Sodium valproate – not clinically significant^{4,5}**AEDs that cause liver enzyme inhibition:**

Sodium valproate – may raise the blood levels of hepatically metabolised drugs, with important effects on some other AEDs, particularly lamotrigine; but this would tend to make hormonal contraceptives more effective, without evidence of any clinically important added risk of adverse effects

Table 6 Contraceptive preparations that inhibit ovulation

Combined hormonal contraceptives

Desogestrel (Cerazette®)

Etonogestrel (Implanon®) – the active metabolite of desogestrel

Medroxyprogesterone acetate (Depo-Provera®)

The combined hormonal contraceptive (CHC) preparations, available in oral, patch and vaginal ring routes of delivery, achieve contraception by giving a sufficient dose of a progestogen with EE, which act synergistically to inhibit ovulation. Although about 100 µg EE is required to inhibit ovulation when given alone,⁶ when combined with an adequate dose of a progestogen to inhibit ovulation, a minimum of 15–20 µg EE orally is needed, for cycle control. Therefore in the absence of enzyme induction, the usual 30 µg EE preparations give some margin of safety. Some progestogen-only preparations also inhibit ovulation at usual doses (Table 6).

In those women taking an EIAED, first consider one of the first three long-acting methods from Table 4, because they are not affected by EIAEDs (Box 1).⁷

Combined hormonal contraceptives (CHCs)

Combined oral contraceptives (COCs)

If long-acting methods are not acceptable, oral contraception can be initiated with combinations containing at least 50 µg EE and an adequate dose of a progestogen. Since the withdrawal from the UK market of Ovran®, there is no 50 µg preparation available in the UK. Norinyl-1®, which contains 50 µg mestranol, is not suitable, because mestranol is a prodrug for EE, and is only 75–80% converted, so that each tablet provides less than 40 µg EE. It is possible to use a 20 µg plus a 30 µg pill to obtain the 50 µg total (NL), as long as the estrogens and progestogens in the two preparations are the same, such as Loestrin-20® plus Loestrin-30®. However it is easier, less confusing and almost certainly more reliable to use two of the same 30 µg preparation (NL), such as two tablets daily of Microgynon-30®, which is the most widely used brand in the UK.

Since there remains a chance that despite higher dosing, the EIAED may impair the anovulatory effect of the COC when the blood levels are at their lowest towards the end of

the 7-day pill-free interval,⁸ it is our recommendation that in addition to taking two pills a day, they should be given in a tricycling or continuous regimen.⁹ Tricycling entails taking three or four cycles of the hormonal contraceptive preparation (two tablets or 60 µg EE per day) consecutively, without a break, followed by a shorter pill-free interval of 4 days (NL). This tricycling regimen is a long-established method of assuring contraceptive efficacy.⁹ The dose should not be increased if breakthrough bleeding occurs early in the first tricycle, because this usually settles during the first 2 to 3 months.⁹ If breakthrough bleeding only occurs towards the end of each tricycle, it may help to change to a two-cycle extended regimen, though still followed by the shortened 4-day pill-free interval. Very rarely, it may be appropriate to increase the dose of oestrogen above 60 µg, but not above 90 µg per day (NL), and only if no alternative effective contraceptive is acceptable and not if there are known risk factors for thrombosis.

A newer approach is to give the same increased dose continuously and indefinitely, unless the woman gets unacceptable breakthrough bleeding, in which case she is empowered to decide to take a short break of 3 or maximum 4 days, then returning to the continuous dosing (NL). The length of time on continuous treatment before breakthrough bleeding occurs is usually reproduced in subsequent cycles. This is an adaptation for EIAED users of so-called 'tailored' pill-taking.^{6,10,11}

Any patient with epilepsy who is not taking an EIAED should be told of this interaction in case her AED regimen is changed to include an EIAED in the future.

If a woman taking an EIAED is switched to a non-enzyme inducing AED, the higher dose of COC should be maintained for a further complete 28-day cycle, because of the carryover effect of enzyme induction.

Patients are often quite concerned about taking larger doses of hormones, fearing a higher incidence of side effects. They should be reassured, by explaining that dose-dependent side effects are related to the circulating blood levels. The larger hormonal doses given in combination with EIAEDs give comparable blood levels to normal pill doses when administered alone. The interaction between EIAEDs and hormone dose should be explained at the time of the consultation, even if it is not raised by the patient, because concern may only arise after the patient gets home and has time to think about it and talk to friends and relatives.

Combined contraceptive patch (Evra®) and vaginal ring (NuvaRing®)

The combined contraceptive patch and vaginal ring are also affected by enzyme induction. Using two patches at a time is not advised,⁷ likewise the use of two rings; therefore patches and rings are not suitable for long-term use on their own by women taking EIAEDs.

Progestogen-only preparations

Progestogen-only pills (POPs)

Progestogens, like estrogen preparations, are also affected by EIAEDs, aggravating other difficulties associated with this form of contraception. POP users starting an EIAED should be advised to consider other forms of contraception, and POPs should in general not be given to women already on an EIAED. Desogestrel (Cerazette®) has an advantage over other oral POPs, especially in younger, more fertile women, because it gives nearly 100% inhibition of ovulation.¹² In addition, it provides a 12-hour 'missed pill window', compared to the usual 3 hours. In women who are not on an EIAED and take desogestrel daily, the blood

Box 1: Summary of contraceptive options for women taking enzyme-inducing antiepileptic drugs (EIAEDs)

- 1 Consider methods of contraception that are not affected by EIAEDs (Table 4).
- 2 If none of these is acceptable, combined oral contraception may be considered:
 - using 50–60 µg ethinylestradiol (NL)
 - either tricycled with a shortened 4-day pill-free interval or taken continuously without a break (NL)
 - using additional contraception (e.g. condoms) until a satisfactory regimen is established.

NL, not licensed.

level of desogestrel normally reaches a peak of 640 pg/ml in less than 2 hours and declines to 119 pg/ml at 24 hours. A blood level of 90 pg/ml is required to inhibit ovulation.¹³ For some women on long-term EIAEDs it might be appropriate to take two tablets daily (NL) of desogestrel (Cerazette). Since most patients on AEDs take their medicines twice a day, one desogestrel tablet should also be taken twice a day, to achieve a smoother 24-hour blood level profile.

Progestogen implant (Implanon®)

EIAEDs are believed to affect the progestogen implant (Implanon®), which contains etonogestrel¹⁴ and should not be given to patients already taking an EIAED. For women who already have an implant and are starting long-term EIAED treatment, removal of the implant after transfer to an alternative long-acting method (Table 4) is usually advised. Some satisfied etonogestrel users may resist this recommendation; an alternative option, though there are no reported studies, would be to take in addition a daily oral desogestrel pill (Cerazette) (NL), or use an additional barrier method, indefinitely. But these suggestions rather defeat the object of the implant and are usually not acceptable to the patient.

Postcoital or emergency contraception

The efficacy of emergency contraception is also affected by EIAEDs.¹⁵ Pharmacists should ask patients about what other medications they are taking. If an EIAED or self-medication, such as St John's Wort, is mentioned, the patient should normally be referred to her physician, who should then either fit a copper intrauterine device (IUD) or, as second choice, prescribe two tablets of hormonal emergency contraception. This could be either two 1.5 mg tablets stat of levonorgestrel (LNG) (Levonelle One Step®, Levonelle 1500®) (NL)¹⁵ or two 30 µg tablets of ellaOne® (NL). ellaOne is a new emergency contraceptive containing ulipristal acetate, which is licensed for use up to 5 days after sexual intercourse.^{16,17}

Medroxyprogesterone acetate (Depo-Provera®)

The problem of enzyme induction does not apply to the use of medroxyprogesterone acetate (Depo-Provera®), whose metabolism is proportional to hepatic blood flow, suggesting a virtually 100% clearance on first pass through the liver.^{18,19} Enzyme induction by EIAEDs can have no additional effect and blood levels are not affected. It is therefore not necessary to alter either the dose or the interval between injections. Irregular, frequent or prolonged bleeding with this depot injection is quite common in women not on EIAEDs, especially in the early months of use. This problem reduces considerably after 1 year and only rarely requires intervention. In patients on an EIAED this effect might be inappropriately ascribed to enzyme induction.

A potential problem in using this depot preparation in adolescent girls is suggested by data showing that this treatment is associated with impairment of the achievement of peak bone mass, which normally occurs in the early twenties. However, the Medicines and Healthcare products Regulatory Agency (MHRA) advises that depot injection may be used as a first-line treatment after discussion of alternatives with the patient, and with reassessment after 2 years.²⁰ There is also the potential problem of weight gain, which should be discussed as it is common with these preparations and very unwelcome in teenage girls. However, the depot injection remains a useful option, and for some women with epilepsy there is an additional

advantage of much less hormonal variation during the menstrual cycle.

Levonorgestrel-releasing intrauterine system (Mirena®)

The levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena®) is not significantly affected by EIAEDs.²¹ It is highly effective and not dependent on good compliance. It is therefore a very suitable option for women with epilepsy, especially those taking EIAEDs, particularly if parous. With good counselling and expertise at the time of insertion, it is also suitable for selected nulliparous women, including adolescents.

Postpartum contraception

The usual advice about the timing of the start of the different contraceptive methods and their suitability after delivery, which should include consideration of breastfeeding, is not affected by prescription of EIAEDs. However, women taking EIAEDs should consider the suitability of different methods and follow the dose protocols outlined above.

Lamotrigine

The co-prescription of lamotrigine with all CHCs is particularly complex. CHCs reduce the blood level of lamotrigine by 40–60%, because estrogens induce the liver enzyme responsible for the glucuronidation of lamotrigine, glucuronyltransferase. However, there is no additional effect if the patient is also taking an EIAED in addition to lamotrigine, because EIAEDs also induce glucuronyltransferase activity and estrogens do not significantly add to this effect.^{22–24}

Therefore, starting a CHC in a patient already on lamotrigine, not in combination with an EIAED, may result in poorer control of the epilepsy. If the epilepsy is not under good control, the dose of lamotrigine should be re-titrated. A small increment in the dose may be all that is required, but in some patients the dose may need to be doubled.

This effect is much more of a problem in patients whose epilepsy is very well controlled, as the addition of a CHC may cause the recurrence of epilepsy and even a single seizure would prohibit driving for a year. In these patients, the increase in the dose of lamotrigine should take place when starting the CHC. However, it is not possible to determine accurately by how much the dose should be increased, or even if it is truly necessary in any individual patient, because of the wide between-patient variation in this effect. Clearly, the alternatives including another contraceptive or a different AED should be discussed.

There is no problem in starting lamotrigine in patients already on CHCs, because the dose of lamotrigine would then be titrated to the patient's needs in the usual way. Lamotrigine has no significant effect on EE concentrations, but does reduce LNG levels by about 20%, which is a potentially significant fall. Though there is no published evidence that lamotrigine alters the contraceptive efficacy of CHCs, in one study²⁴ breakthrough bleeding was observed in 7/16 (32%) subjects when lamotrigine was added to patients taking the COC, though there was no biochemical evidence of ovulation. We now take the precautionary view that tricycling or continuous use at normal doses would be contraceptively safer. Moreover, the shorter hormone-free interval, or no interval, would also usefully minimise or avoid possible side effects from the substantial rise in lamotrigine blood levels that may occur in the usual hormone-free interval.

The effect of lamotrigine on the efficacy of POPs has not been reported, but if lamotrigine reduces other

Box 2: Procedures to follow when prescribing lamotrigine

The following procedures are advised when using lamotrigine; but they are *not* necessary if the patient is also taking an enzyme-inducing antiepileptic drug (EIAED). Blood levels may be helpful because the within-patient variation is much less than the between-patient variation.

- 1 If treatment with lamotrigine is being considered for a woman already using any hormonal method of contraception, aside from the levonorgestrel intrauterine system (LNG-IUS), consider an alternative AED: particularly for women on a progestogen-only preparation whose efficacy might be reduced. Otherwise follow the recommendations above and use the usual AED dose escalation protocol to obtain seizure control.
- 2 If considering a hormonal method of contraception containing an estrogen for a woman already taking lamotrigine, first consider an alternative method of contraception. Otherwise increase the dose of lamotrigine by up to twice the previous dose at the same time as starting a combined hormonal contraceptive (CHC). Note that the blood level of lamotrigine may double in the hormone-free interval and this may cause side effects. To avoid this, we now advise shortening the hormone-free interval, or the use of continuous treatment (NL).
- 3 When stopping a CHC and continuing treatment with lamotrigine, reduce the dose of lamotrigine.
- 4 The progestogen implant (Implanon®), depot medroxyprogesterone acetate and the LNG-IUS are all usable, with no change expected to be necessary in the lamotrigine dose and no established concerns about reduced contraceptive efficacy.

NL, not licensed.

progestogens by 20%, blood levels might fall below adequate contraceptive levels towards the end of 24 hours. Therefore, until further evidence is available, the co-prescription of lamotrigine and a POP cannot be recommended, though two tablets daily of Cerazette should deal with this possible interaction (NL) (Box 2).

In view of these problems, together with the need to increase the dose of lamotrigine substantially during pregnancy and the high levels of lamotrigine that develop in breastfed babies, consideration should be given to using an alternative AED in women of childbearing age.

Conclusions

The effect of liver enzyme induction by some AEDs on most hormonal methods of contraception can be safely and effectively managed using the protocols outlined in this review. The optimal AED for the patient and the type of epilepsy can nearly always be combined with an acceptable method of contraception, but this decision does require careful consideration of the available options and a detailed discussion of the advantages and problems associated with the various combinations.

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Editor's note

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