Which combined oral contraceptive pill is suitable in a patient who is taking hepatic enzyme-inducing drugs, such as carbamazepine, phenytoin, rifampicin or rifabutin?

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Date prepared: May 2019

Background

Combined oral contraceptives (COC) are metabolised in the liver, mainly by CYP3A4 P450 enzymes. (1) COCs have a higher failure rate when women are taking concomitant hepatic enzyme-inducing drugs. Antiepileptic drugs (AEDs) such as carbamazepine, eslicarbazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, topiramate, perampanel and rufinamide are inducers of CYP3A4. (1-3) Rifampicin and rifabutin, which are used to treat tuberculosis, are extremely potent enzyme-inducers and have been observed to cause a five-fold increase in the rate of metabolism of the COC. (4)

The subsequent enzyme induction increases the metabolism of the COC, resulting in a potentially reduced clinical effect. The size of any effect on contraceptive efficacy depends upon the enzyme inducing-drug used, dose of the hormone and the route of administration. Which combined oral contraceptive can be used in a woman using an enzyme-inducing anti-epileptic or anti-tubercle drug?

Answer

Antiepileptic drugs

If a woman is taking a hepatic enzyme-inducing AED short-term (<2 months), this can be managed more flexibly with the use of a minimum of 30 micrograms ethinylestradiol (EE) pill continuously or tricycle with a shortened 3 or 4 day pill-free interval (PFI), for the duration of treatment and for a further 28 days. (4) Additional contraceptive precautions (such as condoms) are also recommended for this method and during this period. (1;4;5) However, ideally it is recommended to change to an alternative method of contraception that is not affected by enzyme-inducing drugs; such as a one-off depot medroxyprogesterone acetate (DMPA) injection which should cover both the duration of treatment and a further 28 days. (1;4)

For longer term use (>2 months) of enzyme-inducing AEDs, the Faculty of Sexual and Reproductive Healthcare (FSRH) suggest that an alternative contraceptive method, such as DMPA, levonorgestrel-releasing intrauterine system (LNG-IUS) or intrauterine devices (IUD), which are not affected by enzyme-inducing AEDs, should be used first line instead of a COC. (1) However, if a woman chooses to use a COC, a daily dose of at least 50 micrograms of oestrogen (usually ethinylestradiol (EE)) should be used (to a maximum of 70 micrograms). This is taken continuously or as a tricycing regimen with a PFI of 4 days for the duration of treatment and a further 28 days. (1-5)

Choice of oral contraceptive

There are no suitable EE 50 microgram preparations available in the UK. Norinyl-1® contains 50 micrograms of the EE prodrug mestranol. (5) The metabolic conversion of mestranol to EE is only about 75%-80%; 37.5 - 40 micrograms of oestrogen is produced, which is less than the 50 microgram recommended minimum. (4)

Although unlicensed, a combination of lower dose pills that contain the same progestogen could be used to obtain the required minimum of 50 micrograms of oestrogen, i.e. a 30 microgram COC plus a 20 microgram COC, or two 30 microgram COCs. (1;4) The additional hormones taken are

metabolised to a greater extent by the liver because of enzyme induction, leaving the same amount in the body as other COC takers would receive from a single COC. (6) The combinations of monophasic COCs listed in table 1 will provide a daily dose of ≥50 micrograms of EE.

Table 1: Monophasic oral contraceptives available in the UK (January 2019). (5)

50mcg ethinylestradiol (20mcg+30mcg)	**60mcg ethinylestradiol (2x30mcg)** i.e. two tablets	**Progestogen**
• Loestrin 20® & Loestrin 30®	Loestrin 30®	Norethisterone
• Mercilon20® & Marvelon30® • Gedarel® 20 & Gedarel® 30	Gedarel 30® Marvelon30®	Desogesterol
• Femodette20® & Femodene30® • Millinette®20 & Millinette® 30 • Sunya 20® & Katya 30®	Femodene® Katya 30/75® Millinette 30/75®	Gestodene
	Levest30® Microgynon 30® Ovranette30® Rigevidon30®	Levonorgesterel

Note that this list is not exhaustive and that the latest edition of the BNF should be consulted for currently available COCs.

Tricycling and pill-free interval

The usual 7 day pill-free interval between packets also weakens the contraceptive effect therefore *in addition* to increasing the daily dose of oestrogen, 3 or 4 cycles of monophasic tablets should be taken without a break ("tricycling" or extended regimen) followed by a short PFI of 4 days. (1-5)

Tricycling and dose doubling of COCs as described above are unlicensed uses. The manufacturer of the chosen contraceptives will not accept liability if a problem should occur. It is important that the patient is aware that the combination of two COCs, along with a shortened pill free interval, is unlicensed and there is less evidence about the effectiveness of this regimen. (5)

Breakthrough bleeding

Breakthrough bleeding can be an indicator of low serum hormone concentrations. (1;3) If breakthrough bleeding occurs, it usually settles during the first two or three months cycles. Otherwise, efficacy cannot be guaranteed and the daily dose of oestrogen may need to be increased (if all other causes of bleeding have been excluded and following specialist advice). (4) The maximum dose of ethinylestradiol that should be used is uncertain. The BNF, FSRH and SIGN suggest a maximum of 70 micrograms daily and NICE guidance states it can be increased to 75 or 100 micrograms per day. Guillebaud recommends a dose of 80 - 90 micrograms daily. (1-3;5) The dose should not be increased if breakthrough bleeding occurs during the first month, as it may subside. If breakthrough bleeding occurs during the third month, Guillebaud advises that it may help to take a bleeding-triggered pill-free break of 3 or 4 days and restart; added precautions are not needed if at least seven pills have been taken since the last PFI. (4;7)

Additional contraceptive methods

As already mentioned, additional precautions such as the use of condoms is recommend if the patient has been prescribed an enzyme-inducing AED short term, and is using a minimum of 30 micrograms of the EE pill continuously or tricycling with a shortened PFI. (1;4;5) With regards to the long term use of enzyme inducing AED, there is no clear recommendation as to whether additional precautions are required when using a COC in the method outlined above.

Anti-tubercule drugs

Rifampicin and rifabutin are more potent enzyme inducers than AEDs and women using these drugs long term (over 2 months) require an alternative method of contraception, i.e. avoiding the COC altogether, even the higher-dose tricycling regimens as explained above. The injectable DMPA, LNG-US or an IUD are therefore suitable alternative options. The alternative method of contraception should be continued for four weeks after stopping the enzyme inducing drug (4;5)

Stopping the enzyme inducing drug

If an enzyme inducing drug has been used for 1-2 months and is then stopped, it can take up to 4 weeks for the liver enzymes to return to normal functionality. (1;2;5) Therefore higher doses of the COC, with or without additional contraceptive protection, should be continued for 4 weeks after stopping the AED. This period should be increased to 8 weeks after more prolonged used of enzyme inducers. In all cases, the PFI should be omitted when switching back to a standard or low-dose COC. (7)

Summary

For women taking very potent enzyme inducers such as rifampicin, the preferred method of contraception would be an IUD, LNG-IUS or an injectable such as DMPA. This is because drugs which induce hepatic enzymes are unlikely to affect the pharmacokinetics of DMPA or LNG-IUS. (4;5)

This method should also be considered as first-line for other enzyme-inducing drugs (such as carbamazepine or phenytoin); however with these there is also some scope to consider other methods instead. (3;4) Choice of an alternative method also depends upon the length of time the patient will be taking the enzyme-inducing drug.

For short term use of enzyme-inducing AEDs (<2 months), a minimum of 30 micrograms ethinylestradiol (EE) pill continuously or tricycle with a shortened 3 or 4 day pill-free interval (PFI), can be used for the duration of treatment and for a further 28 days (with additional precautions such as the use of condoms). (1;3;4)

For longer term use (>2 months) of a hepatic enzyme-inducing AED, a daily dose of at least 50 micrograms of oestrogen (usually ethinylestradiol (EE)) should be used (to a maximum of 70 micrograms). This is taken continuously or as a tricycing regimen with a PFI of 4 days for the duration of treatment and a further 28 days. (1-5)

The use of a COC in both these ways is unlicensed, and it is important to ensure that the patient is made aware of this. The manufacturer of the chosen contraceptives will not accept liability if a problem should occur.

Limitations

- The interaction between COCs and AEDs such as carbamazepine and phenytoin is widely documented but published data are lacking to support the use of a higher dose COC.
- Risk factors for the use of COCs must be taken into account for each patient before prescribing.
- Note that this Q&A is focused on patients taking enzyme-inducing anti-epileptic drugs such as carbamazepine or phenytoin, and drugs used to treat tuberculosis (rifabutin and rifampicin). Though the answer may be suitable for patients taking other enzyme inducing medication, this fact must be taken into account.
- This Q&A does not address the effect of hormonal contraception on levels of anti-epileptic drugs such as lamotrigine.

References

(1) Clinical Guidance: Drug Interactions with Hormonal Contraception. January 2018. Faculty of Sexual and Reproductive Healthcare. Accessed via: https://www.fsrh.org/documents/ceu-clinical-guidance-drug-interactions-with-hormonal/ on 07/01/19.

(2) Diagnosis and management of epilepsy in adults (SIGN 143). May 2015. Revised 2018. SIGN. Accessed via: https://www.sign.ac.uk/sign-143-diagnosis-and-management-of-epilepsy-in-adults on 07/01/2019

(3) The epilepsies (CG 137). The diagnosis and management of the epilepsies in adults and children in primary and secondary care. Phamacological update of Clinical Guideline 20. January 2012 (Last updated April 2018). National Clinical Guidelines Centre for NICE. Accessed via: http://www.nice.org.uk/guidance/CG137 on 07/01/2019.

(4) Guillebaud J, MacGregor A. Contraception. Your questions answered. Seventh edition. Elsevier Limited, 2018.

(5) Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on 01/2019]

(6) Guillebaud J. The pill and other forms of hormonal contraception. Seventh edition. Oxford.: Oxford University Press, 2009: p113.

(7) Guillebaud J. Contraception today. Sixth edition. London.: Informa UK Ltd., 2007: p11-67.

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Date Prepared
May 2019

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Date of check
May 2019

Search strategy
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