

FROM THE CLINICAL EFFECTIVENESS UNIT (CEU)

The members' enquiry service: frequently asked questions

Alison de Souza, MPH, *Research Assistant*; **Susan Brechin**, MRCOG, MFFP, *Unit Co-ordinator*; **Gillian Penney**, FRCOG, MFFP, *Honorary Director, Clinical Effectiveness Unit, Faculty of Family Planning and Reproductive Health Care, London, UK*

Correspondence: Ms A de Souza; FFP CEU, Office 63, Aberdeen Maternity Hospital, Cornhill Road, Aberdeen AB25 2ZD, UK. Tel: +44 (0) 1224 553623. E-mail: ffp.ceu@abdn.ac.uk

(Accepted 26 August 2003)

Journal of Family Planning and Reproductive Health Care 2003; **29**(4): 225–226

Background

In this issue of the *Journal of Family Planning and Reproductive Health Care*, the Clinical Effectiveness Unit (CEU) presents an illustrative response on the evidence for the efficacy of combined oral contraception (COC) in women with epilepsy who take anti-epileptic liver enzyme-inducers. In developing this response, the CEU searched the sources listed below and presents the evidence obtained first from the National Guidelines Clearing House, followed by existing guidance from the Faculty of Family Planning and Reproductive Health Care (FFPRHC) and the Royal College of Obstetricians and Gynaecologists (RCOG). Recommendations from the World Health Organization (WHO) and evidence from the Cochrane Library, MEDLINE and EMBASE are presented subsequently.

Illustrative CEU response

Clinical question

For women with epilepsy who use anti-epileptic liver enzyme-inducers and, after counselling, choose to use COC, which regimen will provide effective contraception?

Summary of response

Women with epilepsy who are using anti-epileptic liver enzyme-inducing medication should be counselled regarding the risks of reduced efficacy of COC. If after counselling they wish to use COC, they should be advised to use a regimen containing at least 50 µg (micrograms) of ethinyl oestradiol or mestranol. Additional barrier contraception should be advised together with high-dose COC. Barrier methods should be continued until 4 weeks after the discontinuation of anti-epileptic liver enzyme-inducing drugs, as enzyme induction persists for this period of time after the medication is withdrawn.

Table 1 Sources used in developing the Member's Enquiry Response

| Source searched | Information identified |
|---|-------------------------|
| National Guidelines Clearing House | See text |
| Existing FFPRHC and RCOG Guidance | See text |
| WHO Publications: <i>Improving access to quality care in family planning: medical eligibility criteria for contraceptive use</i> (2000) and <i>Selected practice recommendations for contraceptive use</i> (2002) | See text |
| The Cochrane Library | No relevant information |
| MEDLINE and EMBASE from 1988 to 2002 | See text |

FFPRHC, Faculty of Family Planning and Reproductive Health Care; RCOG, Royal College of Obstetricians and Gynaecologists; WHO, World Health Organization.

Evidence-based medicine question (which guided our literature search strategy)

Population: Women with epilepsy who use anti-epileptic liver enzyme-inducers.

Intervention: Combined oral contraception (COC).

Outcome: Contraceptive efficacy.

Information sources

The CEU searched the sources listed in Table 1 in developing this Member's Enquiry Response

Epilepsy is a neurological disorder with a lifetime prevalence of between 2% and 5% of the population and an annual incidence rate of 80 per 100 000 with the highest rates being among children and the elderly.¹ It is characterised by recurrent, unprovoked seizures that may be defined as generalised seizures involving both hemispheres of the brain, partial or focal seizures which begin in a defined part of the brain, or status epilepticus, which involves one or more seizures lasting for at least half an hour without recovery of consciousness between each episode.¹

Anti-epileptic drugs inhibit the processes involved in the development of seizures and are grouped according to their main mechanism of action. They include: sodium channel blockers, calcium current inhibitors, gamma-aminobutyric acid (GABA) enhancers, glutamate blockers, carbonic anhydrase inhibitors, hormones and drugs whose mechanism of action remains unknown.² Some anti-epileptic drugs are liver enzyme-inducers and examples of these are carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone and topiramate.³ Other anti-epileptics are non-enzyme-inducers and include acetazolamide, benzodiazepines, ethosuximide, gabapentin, lamotrigine, levetiracetam, tiagabine, valproate and vigabatrin.³

An interaction between anti-epileptic liver enzyme-inducers and the combined oral contraceptive pill (COC) was first proposed when the dose of oestrogen in the COC was reduced from 100 to 50 µg.⁴ A higher incidence of breakthrough bleeding and contraceptive failure was then noted in women with epilepsy compared to women in the general population. A COC containing 50 µg ethinyl oestradiol (Ovran®, Wyeth Laboratories) was discontinued in 2002, although a preparation containing 50 µg mestranol (Norinyl-1®, Pharmacia) remains available.⁵

Evidence reviewed

The National Guidelines Clearing House. A 2003 national clinical guideline on the diagnosis and management of epilepsy in adults by the Scottish Intercollegiate Guidelines Network (SIGN) advises that it is best practice for clinicians to provide contraceptive advice before young women with epilepsy are sexually active, and to encourage these women to plan their pregnancies.³ The guideline development group advises that anti-epileptic drugs that do not induce liver enzymes, are preferable for women who

choose to use oral contraception. Based on non-analytic studies, expert opinion or evidence extrapolated from higher quality studies, SIGN recommends that women who take anti-epileptic liver enzyme-inducers should use a COC containing at least 50 µg oestrogen and increase the dose of oestrogen if breakthrough bleeding occurs with this COC. Tricycling by taking three consecutive packs of the COC with 4 pill-free days should be considered, but no evidence has been identified which shows this to be more effective than monocycling. Additional barrier contraception is recommended in addition to the high-dose COC, and this should be advised until 4 weeks after the anti-epileptic liver enzyme-inducer is discontinued to ensure contraceptive efficacy.³

A guideline from the American Academy of Neurology recommends that clinicians should discuss the risk of contraceptive failure with women taking anti-epileptic enzyme-inducers who choose to use hormonal methods of contraception and document the discussion.⁶ Women who choose to use the COC are advised to use a regimen, which includes at least 50 µg ethinyl oestradiol or mestranol.

Existing FFPRHC and RCOG Guidance. Guidance on first prescription of COC from the FFPRHC CEU,⁵ published in this issue of the Journal, supports the recommendations made by the SIGN guideline above.³ Women using liver enzyme-inducing drugs who, having considered other methods, still choose to use COC should be prescribed a preparation containing 50 µg ethinyl oestradiol or mestranol. Additional barrier contraception is advised until 4 weeks after cessation of the liver enzyme-inducer. As the COC containing 50 µg ethinyl oestradiol has been discontinued, an alternative regimen involving the use of two low-dose COCs (providing a total daily dose of 50–60 µg ethinyl oestradiol) has been proposed in this Guidance document. To date however, no trials have compared the bioavailability of two low-dose COCs taken daily to that of a single daily high-dose pill.

A FFPRHC Aid to Continuing Professional Development Topics (FACT) looks at interactions with hormonal methods of contraception and advises that women taking enzyme-inducers need to use a COC containing at least 50 µg ethinyl oestradiol to ensure contraceptive action.⁷ Efficacy may be further increased by tricycling and/or by decreasing the pill-free interval. The absence of breakthrough bleeding is frequently interpreted as a marker of sufficient contraceptive cover but evidence to support this is lacking in the literature.

WHO Publications. The WHO Medical Eligibility Criteria for Contraceptive Use (WHOMEC) advises that for women who take commonly used drugs, which affect liver enzymes, such as phenytoin, carbamazepine, barbiturates and primidone, the risks of using the COC outweigh the benefits (WHO Category 3).⁸ Although the interaction between liver enzyme-inducers and the COC is not harmful, it is likely to reduce contraceptive efficacy and women who are long-term users of these drugs are encouraged to use other methods of contraception.

MEDLINE and EMBASE from 1990 to 2002. Shorvon et al. determined the frequency of coprescription of anti-epileptic drugs and the COC from 294 computerised general practices in the General Practice Research Database.⁹ A total of 16.7% of the 2341 women with epilepsy aged between 15 and 45 years were using the COC compared to 25% of age-matched women in the general population. Of 200 women taking both an anti-epileptic liver enzyme-inducer and the COC, 56.5% were taking a COC containing less than 50 µg oestrogen and 43.5% were taking a COC containing 50 µg oestrogen or more.

Conflicting evidence was found in the literature on the pharmacokinetics and bioequivalence of ethinyl oestradiol and mestranol. Goldzieher has looked at the pharmacokinetics and metabolism of ethinyl oestrogens and found that variability between populations and individuals may equal or exceed the differences between 35 and 50 µg formulations.¹⁰ The levels of plasma ethinyl oestradiol produced by a 50 µg dose of mestranol were found to be similar to those from a 35 µg dose of ethinyl oestradiol. The author acknowledged that the nature of the oestrogen in the pill might be more important than the dose of the pill used.

Goldzieher and Brody then investigated the pharmacokinetics of ethinyl oestradiol and mestranol and acknowledged that compounds, which undergo an enterohepatic circulation will always exhibit large inter- and intra-individual variability pharmacokinetically.¹¹ Pharmacokinetically, a 50 µg oral dose of mestranol is bioequivalent to a 35 µg dose of ethinyl oestradiol and, depending on the selected endpoint, physiologically mestranol will range from 50% to 100% of the activity of ethinyl oestradiol.

A study by Kisicki looked at the bioequivalence of two COCs containing norethindrone and either ethinyl oestradiol or mestranol compared to two COCs containing a different progestogen in healthy women.¹² Results suggested that the COC containing 50 µg mestranol was bioequivalent to the COC containing 50 µg of ethinyl oestradiol.

Disclaimer

The advice given in this Member's Enquiry Response has been prepared by the FFPRHC Clinical Effectiveness Unit team. It is based on a structured search and review of published evidence available at the date of preparation. The advice given here should be considered as guidance only. Adherence to it will not ensure a successful outcome in every case and it may not include all acceptable methods of care aimed at the same results. This response has been prepared as a service to FFPRHC members, but is not an official Faculty Guidance product; Faculty Guidance is produced by a different and lengthier process. It is not intended to be construed or to serve as a standard of medical care. Such standards are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances. Members are welcome to reproduce this Response by photocopying or other means, in order to share the information with colleagues.

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