

FROM THE CLINICAL EFFECTIVENESS UNIT (CEU)

The members' enquiry service: frequently asked questions

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Introduction

In this frequently asked question, the Clinical Effectiveness Unit (CEU) presents the evidence regarding the timing of depot medroxyprogesterone acetate (DMPA) contraceptive injections for women using liver enzyme-inducers. Although liver enzyme-inducers that may be encountered in clinical practice are listed, clinicians should refer to the relevant section on drug interactions in the *British National Formulary* (BNF) for the most up-to-date list.¹

Illustrative CEU response

Clinical question

For women who use liver enzyme-inducers, what injection interval for DMPA will provide effective contraception?

Summary of response

The progestogen-only injectable contraceptive, DMPA, is cleared at a rate equal to the hepatic blood flow, and is unaltered by liver enzyme-inducers. The Summary of Product Characteristics (SPC) for DMPA states that serum levels of medroxyprogesterone acetate are not reduced by liver enzyme-inducers and there is no need to alter the usual injection interval of 12 weeks. In clinical practice, however, DMPA has been given every 10 weeks to women using liver enzyme-inducers. The evidence to support a more frequent injection interval from the Scottish Intercollegiate Guidelines Network (SIGN) is based on non-analytical studies, expert opinion or data extrapolated from higher quality studies. The World Health Organization (WHO) *Medical Eligibility Criteria for Contraceptive Use* (WHOMEC) recommends that for women using liver enzyme-inducers, the benefits of using DMPA outweigh the risks (WHO Category 2). Clinicians should discuss the lack of evidence for a 10-week DMPA regimen with women using liver enzyme-inducers, and establish that the usual injection interval is 12 weeks. Women using liver enzyme-inducers who are established on a 10-week regimen of DMPA may choose to continue with this injection interval.

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

Population: Women using liver enzyme-inducers.

Intervention: Depot medroxyprogesterone acetate.

Outcome: Timing of the injection interval and contraceptive efficacy.

Information sources

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

Background

Drug-metabolising enzymes are found mainly in the liver, kidneys, gastrointestinal tract, skin and lungs and are classified into either phase I or phase II enzymes according

to their mode of action.² Most phase I metabolism is catalysed by the cytochrome P450 enzymes which are haem-containing, membrane-bound proteins that are highly concentrated in the liver.³ At least 12 cytochrome P450 gene families have been identified in humans and three families (CYP1, CYP2 and CYP3) are involved in the majority of drug biotransformations. Each family is further divided into subfamilies such as CYP3A, which include individual enzymes such as CYP3A4 (the major cytochrome P450 enzyme in adult liver).² Altered drug biotransformation is frequently caused either by induction or inhibition of cytochrome P450 enzymes.^{4,5} Enzyme induction leads to an increased rate of biotransformation and therefore decreased drug concentrations, while inhibition leads to an increase in drug concentrations and possibly drug-induced toxicity.³

Anti-epileptics

Women with epilepsy may use anti-epileptic liver enzyme-inducers such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone and topiramate.⁶ Other anti-epileptics such as acetazolamide, benzodiazepines, ethosuximide, gabapentin, lamotrigine, levetiracetam, tiagabine, valproate and vigabatrin are non-enzyme-inducers.

Antibacterial drugs

Rifampicin may be used for the treatment of brucellosis, Legionnaires disease, staphylococcal infections, tuberculosis and leprosy or for the prophylaxis of meningococcal meningitis and *Haemophilus influenzae* Type b infection.¹ Rifabutin is used for the treatment of non-tuberculous mycobacterial disease and pulmonary tuberculosis, and as prophylaxis against *Mycobacterium avium* complex infection in patients with a low CD4 count.¹ Rifampicin and rifabutin both induce cytochrome P450 enzymes and irregular bleeding and pregnancies have

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

Source searched	Information identified
Existing FFRHC and RCOG Guidance	See text
The National Guidelines Clearing House	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 1996 to 2003	No relevant information

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

been reported in women using rifampicin concomitantly with oral contraceptives.^{7,8}

Antifungal drugs

Griseofulvin is indicated for persistent dermatophyte infections of the skin, scalp, hair and nails and is a liver enzyme-inducer.¹

Antiviral drugs

Patients with human immunodeficiency virus (HIV) may be prescribed protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir) or non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine).¹ Protease inhibitors are metabolised by the cytochrome P450 enzyme system in the liver and have the potential for significant drug interactions. The non-nucleoside reverse transcriptase inhibitors may also interfere with drug metabolism in the liver.¹ Treatment may also involve the use of nucleoside reverse transcriptase inhibitors (zidovudine, abacavir, didanosine, lamivudine, stavudine and zalcitabine), which are not cited in the BNF as interfering with drug metabolism, or combination therapy.

St John's Wort

St John's Wort (*Hypericum perforatum*) appears to induce the metabolic cytochrome CYP3A.⁹ The Committee on Safety of Medicines (CSM) has advised that St John's Wort should not be used with oral contraceptives, indinavir, warfarin, cyclosporin, digoxin and theophylline.¹⁰

Evidence reviewed

Existing FFPRHC and RCOG Guidance. A Faculty Aid to Continuing Professional Development Topics (FACT) from the FFPRHC covers interactions with hormonal contraception.¹¹ In current practice, women taking drugs that may induce liver enzymes are often given DMPA every 10 weeks. The FACT cites the SPC for DMPA,¹² which suggests that no time adjustment is required for the injection interval since the contraceptive hormone is cleared at a rate equal to hepatic blood flow, and is not increased by liver enzyme-inducers.

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) recommends that depot injections of progesterone may be used with liver enzyme-inducing anti-epileptic drugs, but should be given every 10 weeks since efficacy may be reduced after this injection interval.⁶ This recommendation was, however, based on non-analytical studies, expert opinion or evidence extrapolated from higher quality studies.

WHO publications. The WHO Medical Eligibility Criteria for Contraceptive Use (WHOMEC) recommends that women who take commonly used drugs which affect liver enzymes can use DMPA as the benefits outweigh the risks (WHO Category 2).¹³ The WHO Selected Practice

Recommendations for Contraceptive Use (WHOSPR) recommend that repeat DMPA injections should be provided every 3 months (12 weeks).¹⁴ Although the WHOSPR suggests repeat DMPA injections can be given up to 2 weeks early, this is not specifically in relation to the use of liver enzyme-inducers.

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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