



Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit

A unit funded by the FFPRHC and supported by the University of Aberdeen and the Scottish Programme for Clinical Effectiveness in Reproductive Health (SPCERH) to provide guidance on evidence-based practice

FACULTY STATEMENT FROM THE CEU

On

Levonelle® 1500 and the use of liver enzyme inducing drugs

On the 1st of November 2005, Levonelle® 1500 (levonorgestrel 1.5mg) became available as a prescription only medicine (POM) in the United Kingdom. Previously, levonorgestrel was available as two tablets (each 750µg) (Levonelle-2) to be taken together as one single dose within 72 hours of unprotected sexual intercourse or contraceptive failure. This regimen is to be discontinued and the new Levonelle 1500 regimen will become standard.

Previous Faculty of Family Planning and Reproductive Health Care (FFPRHC) guidance has addressed the issue of use of levonorgestrel for emergency contraception for women who are concurrently using liver enzyme inducing drugs. However, Faculty guidance has always been based on the availability of 750µg tablets of levonorgestrel.

In FFPRHC guidance and in the British National Formulary, it is stated that the dose of levonorgestrel should be increased by 50% for women who are using liver enzyme inducing drugs. The increased dose should be taken as a single 2.25mg dose. This recommendation is based on established clinical practice and is outwith the product licence.

No studies have been found to confirm that this dose increase is required. However, due to the consequences should an unintended pregnancy ensue, the CEU currently advises that women who use liver enzyme inducing drugs should take a single dose of levonorgestrel (1.5mg) as soon as possible after UPSI, within 72 hours, and repeat the dose 12 hours later (100% increase in dose). Women should be made aware that this advice is based on clinical judgement and not on research evidence. There are no published studies on compliance or side effects with this regimen and it is outwith the product licence. Women should always be offered the alternative of a copper-bearing intrauterine device which is unaffected by concomitant drug use.

This advice regarding a 100% increase in dose should be viewed as interim. Definitive recommendations on this topic will be provided in formal **FFPRHC Guidance on Emergency Contraception to be published in April 2006.**

Background

On the 1st of November 2005, Levonelle® 1500 (levonorgestrel 1.5mg) became available as a prescription only medicine (POM) in the United Kingdom. Levonorgestrel is administered orally as a means of preventing pregnancy following unprotected sexual intercourse (UPSI) or after contraceptive failure.

Levonorgestrel was licensed in 1999 as Levonelle-2 (POM) and Levonelle (pharmacy supply). Both versions comprised two tablets, each containing 750µg (micrograms) of levonorgestrel. These regimens were based on randomised controlled trials (RCTs) which showed efficacy of the two 750µg levonorgestrel tablets, taken 12 hours apart, within 72 hours of UPSI.^{1,2}

Subsequently, a large multicentre RCT in 2002² found that there was no difference in efficacy when comparing a divided dose (two 750µg tablets) and a single dose of levonorgestrel (1.5mg). It was considered that giving a single dose simplified treatment for women, without an increase in side effects. To reflect this new evidence, a change in the Summary of Product Characteristics for Levonelle-2³ and Levonelle⁴ occurred in 2003, which stated that the two tablets should be taken together, as a single dose, as soon as possible within 72 hours of UPSI. In October 2004, the divided dose of pharmacy levonorgestrel was discontinued and replaced with a single 1.5mg dose (Levonelle One-Step)⁵. POM of Levonelle from November 2005 will become one single, round tablet, containing 1.5mg levonorgestrel (Levonelle 1500).⁶

Previous Faculty of Family Planning and Reproductive Health Care (FFPRHC) guidance has addressed the issue of use of levonorgestrel for emergency contraception for women who are concurrently using liver enzyme inducing drugs.^{7,8} However, Faculty guidance has always been based on the availability of 750µg tablets of levonorgestrel.

With the release of Levonelle 1500, the CEU aims to review current evidence to identify how women who use liver enzyme inducing drugs should be managed, and what dose of levonorgestrel should be given.

Evidence reviewed

FFPRHC published guidance in April 2005 entitled '*Drug interactions with hormonal contraception.*' The guidance contained a table of all drugs that are known to induce liver enzymes. This table is replicated on the next page (table 1).

Drugs that induce liver enzymes (see table 1) are used to treat a number of conditions and may reduce the efficacy of hormonal contraception by increasing the metabolism of EE and progestogens.⁷ The Summary of Product Characteristics for levonorgestrel does not indicate what dose should be administered to women who use liver enzyme inducers. Presently, the British National Formulary⁹ recommends that the dose of levonorgestrel should be increased by 50% for women who are using liver enzyme inducing drugs. This should be taken as a single 2.25mg dose. This recommendation is based on established clinical practice and is outwith the product licence.¹⁰ No studies have been found to confirm that this increase in dose is required.

This regimen will no longer be applicable when only 1.5mg tablets are available (Levonelle One-Step and Levonelle 1500). Despite extensive searching, it still remains that there is no evidence to confirm that an increase in dose is necessary. However, due to the consequences should an unintended pregnancy ensue, the CEU advises that women who use liver enzyme inducing drugs should take a single dose of levonorgestrel (1.5mg) as soon as possible after UPSI, within 72 hours and repeat the dose 12 hours later (100% increase in dose). Women should be made aware that this advice is based on clinical judgement and not on research evidence. There are no published studies on compliance or side effects with this regimen and it is outwith the product licence. Women should always be offered the alternative of a copper-bearing intrauterine device, which is unaffected by concomitant drug use.

Table 1 *Drugs that induce liver enzymes*

Type of Drug	Liver enzyme induction	Effect
<i>Anti-Epileptic</i> Oxacbazepine Phenytoin Phenobarbital Primadone Topiramate	Carbamazepine	Reduction in ethinylestradiol (EE) and progestogens ¹¹⁻¹⁴
<i>Antibiotic</i>	Rifampicin Rifabutin	Reduction in EE and progestogen, breakthrough bleeding ^{9;15;16}
<i>Antifungal</i>	Griseofulvin	Known to be a potent liver enzyme-inducer, pregnancies documented ¹⁷
<i>Antiretroviral</i>	<i>Protease inhibitors</i> Ampernavir Atazanavir Nelfinavir Pinavir Saquinavir Ritonavir	Reduction in EE and progestogen but additional or alternative contraceptive methods advised with hormonal contraception ¹⁸ EE reduced ¹⁹
	<i>Non-nucleoside reverse transcriptase inhibitors</i> Efavirenz Nevirapine	Reduction in EE and progestogen but additional or alternative contraceptive methods advised with hormonal contraception ¹⁸
<i>Gastrointestinal</i>	Lansoprazole	Can induce liver enzymes but no reduction in EE ²⁰
<i>Immunosuppressant</i>	Tracolumus	Can induce liver enzymes but no published evidence of reduced contraceptive efficacy
<i>Respiratory</i>	Boesntan	Induces liver enzymes but no evidence published for efficacy and hormonal contraception
<i>Central nervous system</i>	Modafinil	Known liver enzyme inducer ^{9;21}

In Summary

Shortly, levonorgestrel will only be available as 1.5mg tablets, both for POM and pharmacy supply. Currently, women who are using liver enzyme inducing drugs who require levonorgestrel for emergency contraception are advised to increase the dose by 50% to 2.25mg. However, this will no longer be possible, as the 0.75µg tablets will not be made by the manufacturers (Schering Health Care). Past advice has been based on established clinical practice, as there is a lack of evidence regarding the concurrent use of oral contraception and liver enzyme inducing drugs. The CEU advises, based on the consequences of unwanted pregnancy, that women should take 1.5mg of levonorgestrel as soon as possible, within 72 hours of UPSI and repeat the dose 12 hours later (100% increase in dose). Women should be informed that there is no data on compliance or side effects of this regimen and its use is outwith the product licence. Women should be offered a copper-bearing intrauterine device as an alternative as this is unaffected by concomitant drug use.

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