

Pharmacokinetic Drug Interactions with Hormonal Contraception

There are two main types of hormonal contraceptives: the combined oral contraceptives (COC), available as tablets which contain both an oestrogen (usually ethinylloestradiol) and a progestogen; and the progestogen-only contraceptives, available as tablets, sub-dermal implants, depot injections and intra-uterine devices. The aim of this bulletin is to highlight some of the clinically important pharmacokinetic drug interactions with hormonal contraception. Further details and advice can be obtained from the Drug Information Service on 03 364 0900 (external), or 80900 (internal).

Pharmacokinetic drug interactions mainly involve alteration of clearance, but also oral availability (absorption and first-pass metabolism), and distribution of either drug. This results in altered concentrations and often changes the effectiveness for a given dose of the affected drug.

Mechanisms of drug interactions affecting contraception

Absorption: Oral ethinylloestradiol and progestogens are absorbed from the small intestine. Absorption can be reduced by drugs that alter gut transit time or cause severe vomiting and/or diarrhoea; additional barrier contraception may be required.

Metabolism: The major route for hepatic metabolism of ethinylloestradiol is hydroxylation, primarily by the cytochrome P450 (CYP) enzyme CYP3A4 but also CYP1A2. Progestogens are substrates for CYP3A4 and CYP219.

Interactions with enzyme-inducing drugs

Drugs that induce CYP3A4, CYP1A2 or CYP2C19 (examples in Table 1) accelerate the metabolism of ethinylloestradiol or progestogens and increase their clearance. Serum concentrations are reduced and contraceptive efficacy can also be reduced, see Table 2 for advice. Enzyme induction may occur within two days and is generally maximal within a week of ongoing use of an inducer. Enzymes gradually return to previous levels of activity in around two weeks after cessation of the drug.

Table 1: Examples of enzyme-inducing drugs

Category	Enzyme-inducing drugs
Antiepileptic	carbamazepine, phenobarbitone, phenytoin, primidone, topiramate [topiramate is a weak inducer; contraceptive efficacy may be unaffected at low doses (< 200mg daily)]
Antibacterial	rifabutin, rifampicin
Antiretroviral	efavirenz, nevirapine
Other	modafinil, aprepitant, prednisone, dexamethasone, pioglitazone, St John's wort

Interactions with enzyme-inhibiting drugs

Drugs that inhibit CYP3A4, CYP1A2 or CYP2C19 enzymes have the potential to decrease the metabolism of oestrogens and progestogens. The clinical significance of this is unclear. If the resultant increased concentration of contraceptive hormones causes side effects (e.g. nausea, headaches), a lower dose can be tried. Enzyme inhibiting drugs include: ritonavir, indinavir, nelfinavir, clarithromycin, itraconazole and ketoconazole.

Excretion and enterohepatic circulation: After metabolism, conjugates of ethinylloestradiol are excreted into the bile and are hydrolysed by enzymes from colonic bacteria in the intestine. This releases active drug to be reabsorbed and theoretically contributes to overall oestrogen concentrations and contraceptive efficacy.

Interactions with antibacterials (non-enzyme inducers)

Antibacterial drugs were thought to affect the enterohepatic recycling of oestrogen, reducing COC efficacy, and increasing the risk of pregnancy. However, there is no strong evidence to support this hypothesis, and recent guidance [1] recommends that additional contraceptive precautions are not required when using hormonal contraception with broad spectrum antibacterials that are not enzyme inducers.

COC affecting the concentrations of other drugs

Ethinylloestradiol may inhibit CYP1A2 and CYP2C19 and thereby increase serum concentrations of drugs metabolised by these routes e.g. clozapine, omeprazole. The glucuronidation of lamotrigine can be induced by ethinylloestradiol, reducing lamotrigine concentrations and leading to increased seizure frequency. Lamotrigine side effects may increase in the pill-free week or when discontinuing a COC. Lamotrigine monotherapy in conjunction with COC use is discouraged as the risks generally outweigh the benefits. When lamotrigine is combined with sodium valproate, no reduced effect occurs from concomitant COC use.

Table 2: Advice for women using enzyme-inducing drugs long term [1]

Contraceptive method	Advice for women using enzyme-inducing drugs long-term (>2 months), or within 28 days of stopping enzyme-inducing drugs
Combined Oral Contraception (COC)	Change to an alternative method unaffected by enzyme-inducing drugs (recommended option) Or: use two COC pills containing at least a combined total of 50 micrograms ethinylloestradiol. Use an extended or tricycling regimen with a hormone-free interval of 4 days NB: Not recommended if using rifampicin or rifabutin
Progestogen-Only Contraception	
Oral tablets	Change to an alternative method unaffected by enzyme-inducing drugs
Subdermal levonorgestrel implant (Jadelle®)	Change to an alternative method unaffected by enzyme-inducing drugs
Depot injection medroxyprogesterone acetate (DMPA) (Depo-Provera®)	No change required. Efficacy is unaffected by enzyme-inducing drugs and women can continue with the usual dose and frequency DMPA metabolism is dependent on blood flow to the liver rather than metabolic capacity
Levonorgestrel-releasing intrauterine system (Mirena®)	No change required. Efficacy is unaffected by enzyme-inducing drugs Most of the contraceptive effect is mediated via the direct release of progesterone into the uterine cavity
Emergency contraception (EC)	If hormonal EC is required, 3mg levonorgestrel (2x1.5mg as a single dose- unlicensed) should be taken as soon as possible within 120 hours of unprotected intercourse (unlicensed timescale)

Ref: [1] UK Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Drug Interactions with Hormonal Contraception. January 2011 (updated Sept 2011) accessed 11/10/11 <http://www.fsrh.org/pdfs/CEUGuidanceDrugInteractionsHormonal.pdf>