Combined oral contraception and broad-spectrum antibiotic use

The combined oral contraceptive (COC) is among the most widely used methods of contraception worldwide. The COC is easy to use and extremely effective. Women using the COC may sooner or later require an antibiotic, raising the concern of the unsought COC-antibiotic interaction that may decrease efficacy of the COC and lead to an unwanted pregnancy. In order to address the COC-antibiotic interaction and its potential risk adequately, some knowledge of COC metabolism is required.

COC metabolism

Ethinyloestradiol is used almost exclusively in oral contraceptives in combination with progestogens. The metabolism of the COC is complicated. Most important is the fact that ethinyloestradiol undergoes eventual enterohepatic recirculation. Initially, ethinyloestradiol is subject to first-pass metabolism in the gut mucosa and liver. In the gut wall it is conjugated with sulphate before transport to the liver. In the liver, the hormone is glucuronidated predominantly by the cytochrome P4503A4 enzyme, and secreted in the bile to render ethinyloestradiol inactive and unabsorbable.

Instead of being excreted via the gut, the metabolites may be hydrolysed by enzymatic activity of the gut bacteria (principally *Clostridium* species) to liberate active ethinyloestradiol from the sulphate and glucuronide groups. Ethinyloestradiol can then be reabsorbed in the small intestine to help maintain its therapeutic concentration in the circulation.

Potential mechanisms for COC-antibiotic interactions include mainly antibiotic induction of liver enzymes and the reduction of enterohepatic recirculation of oestrogen.

Liver enzyme induction

Drugs that induce hepatic enzymes, especially cytochrome $P_{450}3A4$, may increase the metabolism of COCs and are associated with COC failure. Although many drugs induce hepatic enzymes and cause COC failure, the only antibiotic of concern is rifampicin. It has been well demonstrated that rifampicin accelerates the metabolism of both ethinyloestradiol and progestogens and potential failure of both COC and the progesterone-only pill.

Reduced enterohepatic recirculation

Theoretically, broad-spectrum antibiotics might temporarily eradicate the gut flora responsible for the deconjugation of ethinyloestradiol metabolites interrupting the enterohepatic recirculation. In practice the interaction between broad-spectrum antibiotics and COCs seems doubtful. To date, limited retrospective surveys with multiple limitations have been conducted on patients from outpatient clinics evaluating possible interactions between antibiotics and COCs. The American Council on Scientific Affairs (see further reading – Dickinson *et al.*) analysed pooled data and concluded that COC failure rates of 1.2 - 1.6% were found in women who were concomitantly treated with antibiotics. Although lower than the ideal failure rates predicted with perfect compliance, they are well within the range encountered with typical use. Multiple individual case reports implicate antibiotics prescribed to women using COCs as the cause of COC failure in compliant patients, but caution should be exercised in data interpretation because of recall bias and underreporting of poor compliance when confronted with an unplanned pregnancy.

Non-enzyme-inducing antibiotics have no effect on the progesterone-only pill since the progestogenic metabolites that are reabsorbed after the cleaving by gut bacteria are biologically inactive.

The above are theoretical mechanisms for COC failure when used together with antibiotics. It should be noted that there is little evidence of increased rates of COC failure in patients treated with antibiotics despite the extensive use of COC. In order to assist prescribers, clear recommendations are presented.

Recommendations

Rifampicin potently induces the hepatic metabolism of COCs, and extra contraceptive methods should be employed. Rifampicin is such a potent enzyme inducer that when given for only 2 days (to eliminate carriage of meningococcus), increased metabolism of ethinyloestradiol must be assumed for the following 4 weeks. Additional non-hormonal contraceptive cover should be used for that time. An alternative method of contraception to the COCs should be considered when treating patients with long-term rifampicin.

The jury is still out whether reduced enterohepatic circulation of COCs caused by disrupted gut flora is fact or textbook theory. Nonetheless, despite the shortage of convincing evidence linking antibiotic use with COC failure, it is possible that some individuals may be more prone to the COC-antibiotic interaction. Women more susceptible to COC failure when using antibiotics cannot currently be identified by any routine diagnostic tests. Given the serious consequences of unwanted pregnancy, a cautious approach is advisable when prescribing a short-term broad-spectrum antibiotic to women using COC. These patients should be informed about the small risk of interactions with antibiotics and, when not comfortable with the risk, should be counselled about the use of additional non-hormonal contraceptive methods. It is generally accepted that additional non-hormonal contraception should be used for the duration of antibiotic treatment and continued for 7 days after the last antibiotic dose. Should the 7 days run beyond the end of the COC pack, the next COC pack should be started with omission of the pill-free interval. Antibiotic courses exceeding 2 weeks allow gut bacteria to develop antibiotic resistance. Extra contraception precautions need to be continued only for the first 2 weeks and an additional 7 days (3 weeks in total) with elimination of the next pill-free interval. Should the first 2 weeks of antibiotic use extend into the last 7 days of the pack, eliminate the next pill-free interval as well.

Further reading

Burroughs KE, Chambliss ML. Antibiotics and oral contraceptive failure. *Archives of Family Medicine* 2000; 9(1): 81-82.

Dickinson BD, Altman RD, Nielsen NH, Sterling ML. Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001; 98(5 Pt 1): 853-860.

Guillebaud J. *Contraception: Your Questions Answered.* 5th ed. Philadelphia (USA): Elsevier Limited, 2009.

Oesterheld JR, Cozza K, Sandson NB. Oral contraceptives. *Psychosomatics* 2008; 49(2): 168-175.

Weaver K, Glasier A. Interaction between broad-spectrum antibiotics and the combined oral contraceptive pill. A literature review. *Contraception* 1999; 59(2): 71-78.

ERIC DECLOEDT, *MB ChB, BSc Pharmacology (Hons)*

MARC BLOCKMAN, *MB ChB, BP-harm, Dip Int Res Ethics, MMed (Clin Pharmacol), FCCP (SA)*

Department of Internal Medicine, Division of Clinical Pharmacology, Groote Schuur Hospital, University of Cape Town

Corresponding author: Eric Decloedt (eric.decloedt@uct.ac.za)