

Antibiotic and oral contraceptive drug interactions: Is there a need for concern?

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OBJECTIVE: To assess the clinical significance of antibiotic and oral contraceptive drug interactions.

DATA SELECTION: MEDLINE search from 1975 to 1998 (September) inclusive. Search terms 'antibiotic', 'oral contraceptive' and 'pregnancy' were included. Published papers as well as references from these papers were reviewed. Papers documenting mechanistic interactions between antibiotics and oral contraceptives were included.

DATA EXTRACTION: Studies reporting oral contraceptive pharmacokinetics, mechanisms, incidence, implicated antibiotics and clinical consequences of antibiotic/oral contraceptive drug interactions.

DATA SYNTHESIS: Reports of oral contraceptive failure seem to be most numerous in women using preparations containing 30 µg of ethinylestradiol and 150 µg of levonorgestrel. Rifampin is the only antibiotic that has been reported to reduce plasma estrogen concentrations. When taking rifampin, oral contraceptives cannot be relied upon and a second method of contraception is mandatory. Amoxicillin, ampicillin, griseofulvin, metronidazole and tetracycline have been associated with contraceptive failure in three or more clinical cases. When these agents are used, the clinician should discuss the available data with the patient and suggest a second form of birth control. Other antibiotics are most likely safe to use concomitantly with oral contraceptives.

CONCLUSIONS: Rifampin is the only antibiotic to date that has been reported to reduce plasma estrogen concentrations. Oral contraceptives cannot be relied upon for birth control while taking rifampin.

Key Words: Antibiotics; Drug interactions; Oral contraceptives; Pregnancy

Interactions des contraceptifs oraux avec les antibiotiques : Doit-on s'inquiéter ?

OBJECTIF : Évaluer la portée clinique des interactions des contraceptifs oraux avec les antibiotiques.

SÉLECTION DES DONNÉES : Recherche dans Medline des articles publiés entre 1975 et septembre 1998 inclusivement. Il s'agissait de rechercher notamment les mots-clés « antibiotique », « oral contraceptive » et « pregnancy ». Les articles publiés, de même que les références accompagnant ces articles, ont été passés en revue. Les articles faisant état des mécanismes de l'interaction entre les antibiotiques et les contraceptifs oraux ont été inclus dans l'étude.

EXTRACTION DES DONNÉES : Études rapportant la pharmacocinétique des contraceptifs oraux, les mécanismes, l'incidence, les antibiotiques impliqués et les conséquences cliniques des interactions des contraceptifs oraux avec les antibiotiques.

SYNTHÈSE DES DONNÉES : Les cas rapportés d'échec des contraceptifs oraux semblent plus nombreux chez les femmes utilisant des préparations contenant 30 µg d'éthinylestradiol et 150 µg de lévonorgestrel. La rifampine est le seul antibiotique qui a été signalé comme agent réducteur des concentrations plasmatiques d'œstrogènes. En cas de prise concomitante de rifampine et de contraceptifs oraux, une deuxième méthode de contraception est indispensable.

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L'amoxicilline, l'ampicilline, la griséofulvine, le métronidazole et la tétracycline ont été associés à un échec de la contraception dans trois cas cliniques et plus. Lorsque ces agents sont prescrits, le clinicien devrait informer les patientes à l'aide des données disponibles et proposer une deuxième méthode de contraception. Les autres antibiotiques peuvent probablement en toute sécurité être administrés en concomitance avec des contraceptifs oraux.

CONCLUSIONS : La rifampine est actuellement le seul antibiotique que l'on a signalé comme agent réducteur des concentrations plasmatiques d'œstrogènes. Pendant un traitement avec de la rifampine, les contraceptifs oraux ne sont pas fiables pour garantir la contraception.

A controversial issue in infectious diseases and obstetrics is whether there is an interaction between antibiotics and oral contraceptives that results in reduced efficacy of the birth control agents. This issue remains an important question in the minds of clinicians because the majority of reports to date are anecdotal and studies performed have been inconclusive.

In North America, oral contraceptives are used by millions of women on a routine basis. This represents nearly 20% of all women between the ages of 15 and 44 years (1). Thus, even if the antibiotic interaction with oral contraceptives is relatively rare, the absolute number of women affected may be substantial.

ORAL CONTRACEPTIVE STEROID PHARMACOKINETICS

The estrogens most commonly found in oral contraceptive preparations are ethinylestradiol and mestranol, a prodrug which is metabolized to ethinylestradiol. After metabolism via the first pass effect, ethinylestradiol has an oral bioavailability of 40% to 50% (2). Hydroxylation is the main metabolic pathway for ethinylestradiol, whereas conjugation is considered to be a minor pathway in most women, resulting in sulphation or glucuronidation of the original estrogenic steroid. Glucuronide and sulphate conjugates reach the small intestine by way of the bile duct. Hydrolytic enzymes of intestinal bacteria break the conjugates down, resulting in the release of free, active estrogenic hormone. The active hormone is then available for reabsorption and undergoes enterohepatic cycling, which is responsible for plasma estrogen levels necessary for contraception.

The enzyme responsible for hydroxylation of the estrogen molecule is cytochrome P450 IIIA4 (CYP3A4) and is under polymorphic genetic control (3). As a result, women are able to hydroxylate ethinylestradiol to varying degrees. Therefore, when trying to evaluate which women are at risk for the oral contraceptive and antibiotic drug interaction, the extent to which women can hydroxylate ethinylestradiol is of prime importance because it is only that estrogen which has not been hydroxylated that is available for subsequent conjugation (4). This is significant because only the conjugated hormone can be hydroxylated in the intestine and then enterohepatically recycled to maintain plasma estrogen levels. Unfortunately, at the present time, there is no method to determine which women are at risk.

The progestins present in oral contraceptive pills (eg, levonorgestrel, norethisterone, desogestrel, gestodene, norgestimate) also undergo conjugation. Hydrolysis of conjugates leads to the formation of inactive metabolites because the parent molecule cannot be directly conjugated. Progestins are not

thought to undergo extensive enterohepatic cycling and are, thus, less likely to be involved in drug interactions with antibiotics than ethinylestradiol (5).

MECHANISMS OF INTERACTION

Antibiotics are suspected to diminish oral contraceptive efficacy by two main mechanisms: induction of the cytochrome P450 group of hepatic microsomal enzymes and interference with enterohepatic cycling of ethinylestradiol (6) (Table 1). The former mechanism is thought to be most clinically significant and the most well studied. Rifampin induces cytochrome P450 enzymes in the liver, which results in increased hepatic hydroxylation of estrogens. In fact, the metabolism of estrogens is increased fourfold, resulting in both reductions in area under the curve and increased clearance (4,7,8) (Table 1). However, the data remain incomplete with respect to these pathways and other antibiotic and oral contraceptive interactions.

Antibiotics can interrupt the enterohepatic cycling of estrogens by reducing the bacterial population of the small intestine, which is responsible for hydrolysis of the glucuronide moiety (estrogen metabolite found in bile) to free drug (6). When the gut flora are altered, enterohepatic circulation is reduced, the metabolite is excreted, resulting in lower circulating concentrations of ethinylestradiol. Many antibiotics are believed to decrease oral contraceptive efficacy in this manner, including penicillins, cephalosporins, tetracyclines, macrolides, antifungals, metronidazole, sulphonamides and anti-tuberculosis agents (9) (Table 1).

CONSEQUENCES AND INCIDENCE

Broad spectrum antibiotics can lead to lower levels of circulating oral contraceptive hormone levels and have, thus, been implicated in causing failures in women taking oral contraceptives (10). Failure of oral contraceptive steroids can lead to several outcomes, including breakthrough bleeding, pregnancy and menstrual abnormalities such as amenorrhea and spotting (11). Intermenstrual bleeding is often considered a clinical sign of oral contraceptive failure if it has not been experienced by the patient before with a particular medication (11).

IMPLICATED ANTIBIOTICS

Rifampin, an antituberculosis, antistaphylococcal agent, was first reported to decrease oral contraceptive efficacy through the induction of hepatic enzymes (12). Since then, numerous case reports have been reported implicating rifampin as the cause of oral contraceptive failure resulting in pregnancy, spotting, intermenstrual bleeding or amenorrhea

TABLE 1
Review of reported antibiotic/oral contraceptive drug interactions

Antibiotic class	Specific antibiotic	Oral contraceptive component	Mechanism of interaction	Comment
Penicillins	Ampicillin	Ethinylestradiol/levonorgestrel (Min-Ovral [Wyeth-Ayerst Canada Inc, St Laurent, Quebec], Triphasil, [Wyeth-Ayerst])	Interruption of the enterohepatic cycling of ethinylestradiol by means of reducing the bacterial population of the small intestine, which is responsible for the hydrolysis of the conjugated hormone. The inhibition of hydrolysis can lead to an increased fecal loss of the hormone, resulting in lower circulating levels of ethinylestradiol	No effect on plasma estrogen concentration in controlled studies
Cephalosporins				
Tetracyclines	Doxycycline	Ethinylestradiol/norethindrone (Ortho-Novum 1/35 [Janssen-Ortho Inc, Toronto, Ontario])		Study showed decreased ethinylestradiol levels but not statistically significant. No ovulation noted
	Minocycline	Ethinylestradiol/levonorgestrel & ethinylestradiol and ethynodiol diacetate (Demulen 1/35 [Serle Inc, Toronto, Ontario])		
	Tetracycline	Ethinylestradiol/norethindrone (Ortho-Novum 1/35)		
Sulphonamides	Co-trimoxazole (sulfamethoxazole and trimethoprim)			Actually shown to increase ethinylestradiol levels. Possibly by inhibiting hepatic metabolism. May not require same precautions
Macrolides	Erythromycin			
Antiprotozoal agents	Metronidazole			
Antituberculosis agents	Rifampin	Ethinylestradiol/norethindrone (Ortho-Novum 1/35)	Induction of cytochrome P450 group of hepatic microsomal enzymes	Increases metabolism of both estrogen and progesterone component. Only antibiotic and oral contraceptive interaction that has been proven
	Isoniazid		Unknown	Implicated in 14 pregnancies, but rifampin co-administered in all cases
Antifungal agents	Griseofulvin		Induction of cytochrome P450 group of hepatic microsomal enzymes	Decreases progesterone and estrogen concentrations
	Fluconazole	Ethinylestradiol/norgestrel (Ovral [Wyeth-Ayerst])	Unknown mechanism of interaction. Unlikely related to metabolism because these agents inhibit hepatic oxidase enzymes	No pharmacokinetic interaction detected in study
	Ketoconazole			Believed to interact in same manner as fluconazole and itraconazole. Potent inhibitor of cytochrome P450 system, therefore, inhibits metabolism of oral contraceptives
	Intraconazole	Ethinylestradiol/levonorgestrel (Min-Ovral, Triphasil)		

Adapted from references 2,4,6-11,13,16-23

(11). Isoniazid, another antituberculosis agent, has been reported as the cause of 14 pregnancies; however, rifampin was coadministered in all these cases (10) (Table 1). For other antimicrobial agents, the data are not nearly as convincing. Nevertheless, individual case reports and small, retrospective studies have led to the inclusion of warnings in the *Compendium of Pharmaceuticals and Specialties* (13) and other references about possible interactions between oral contraceptives and

other antibiotics. Prospective studies are lacking or inconclusive for these antibiotics (2,4,6,10). With a recognized failure rate of 1% or less/year in women taking oral contraceptives as directed and 3%/year in typical populations, thousands of pregnancies occur each year in the millions of women taking oral contraceptives. It is not surprising that many of these women are concomitantly being treated with antibiotics (14-16).

A correlation exists between griseofulvin and oral contraceptive failure because four women experienced recurrence of original symptoms (intermenstrual bleeding, amenorrhea) upon re-exposure to the antifungal agent (17) (Table 1). It appears that with terbinafine (Lamisil, Novartis Pharmaceuticals Canada Inc, Dorval, Quebec), a newer oral antifungal agent, the significance of this interaction is lessened (4).

Numerous antibiotics have been implicated in causing oral contraceptive failure by means of interfering with the enterohepatic recirculation of ethinylestradiol (Table 1). The two groups of antibiotics most commonly involved in the contraceptive failures are tetracyclines and penicillins, namely ampicillin. Both ampicillin and tetracycline have been shown to affect plasma and urinary concentrations of estrogen in both pregnant and nonpregnant women, while progesterone levels remain constant (18-20). Later studies in women did not show this, and serum concentrations of ampicillin in humans have not been shown to change significantly the enterohepatic circulation of estrogen (21-23). In a recent study of tetracycline 500 mg every 6 h, in conjunction with ethinylestradiol and norethindrone, the plasma levels of both steroids were not significantly changed within the first 24 h or after five to 10 days (24).

It has been reported that co-trimoxazole (trimethoprim/sulphamethoxazole) actually significantly increases the plasma concentrations of ethinylestradiol (2). The mechanism involved is thought to be an inhibition of hydroxylation of ethinylestradiol by the sulphonamide component of co-trimoxazole. This mechanism would actually decrease the likelihood that co-trimoxazole may lead to oral contraceptive failure. Co-trimoxazole may be the antibiotic of choice in women on oral contraceptives based on this information; however, it must not be forgotten that it has been implicated in 17 pregnancies (4). The evidence implicating neomycin and erythromycin is even more scarce (25).

Studies performed in humans to demonstrate decreased oral contraceptive efficacy as a result of antibiotics have been unable to show an interaction exists, with the exception of CYP3A4 induction by rifampin. Because many of the data are conflicting and inconclusive, it has been difficult to categorize appropriately and discuss the risks with patients. This issue is further complicated because there are also scattered case reports associating multivitamins, anticonvulsants, antihistamines and anti-inflammatory drugs, as well as antibiotics, with reduced oral contraceptive efficacy (10,26,27).

RECOMMENDATIONS

Reports of oral contraceptive failure seem to be most numerous in women using preparations containing 30 µg of ethinylestradiol and 150 µg of levonorgestrel (27). Oral contraceptive drug interactions are thought by some to be more significant in women taking low dose preparations, although much controversy exists (28). Thus, one potential solution may be to increase the amount of ethinylestradiol in the preparation. However, because the majority of women will not be on antibiotics for the long term and increasing the estrogen

TABLE 2
Categories of antibiotics

Category	Drugs
A: Antibiotic that likely reduces birth control pill effectiveness	Rifampin
B: Antibiotics associated with oral contraceptive failure in three or more cases reports	Ampicillin Amoxicillin Griseofulvin Metronidazole Tetracycline
C: Antibiotics associated with oral contraceptive failure in at least one case report	Cephalexin Clindamycin Dapsone Erythromycin Isoniazid Phenoxyethylpenicillin Trimethoprim/sulphamethoxazole

Adapted from reference 29

content of the pill carries an increased risk of thromboembolic disorders, this solution seems somewhat impractical and potentially harmful. Because antibiotics are generally prescribed on a short term basis, another approach to deal with this interaction is to discuss the use of alternative methods of contraception with women who are prescribed antibiotics and are concurrently taking oral contraceptives.

A practical approach suggested by Miller et al (29) is to divide the antibiotics into three groups (Table 2).

Rifampin (Table 2, category A) is the only antibiotic to date that has been shown to reduce plasma estrogen levels. Oral contraceptives should not be relied upon for birth control while taking rifampin. A second method of contraception is necessary, and it is crucial to inform the patient of the chance for an interaction.

Antibiotics in category B (Table 2) have infrequently been linked with reduced oral contraceptive effectiveness. Retrospective case studies have contributed a large portion of information regarding these antibiotics, and a definite interaction is, as yet, unproven. The clinician should discuss the available data with the patient and offer a second form of birth control to patients who request it.

The antibiotics in category C (Table 2) have only rarely been associated with reduced oral contraceptive efficacy and are most likely safe to use concomitantly with oral contraceptives.

There is no way to determine which women are at risk, and, thus, some believe all women should be counselled regarding this interaction and the precautions they can take to avoid any unwanted pregnancy (30). The patient should decide on the alternative method of contraception because she must be comfortable with the method chosen (30).

Clearly, this controversial issue affects millions of North American women annually, yet poor data are available with which to base recommendations. We should ensure that all efforts are made to collect reliable information on failure rates with and without antibiotics. Until then, a practical approach to antibiotic treatment in women taking oral contraceptives is encouraged.

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