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Oral contraceptive steroids – pharmacological issues of interest to the prescribing physician

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Abstract

Oral contraceptive steroids (OCS) are well absorbed from the gastrointestinal tract in humans. However, while the progestogens are almost completely bioavailable, ethinylestradiol (EE_2) is subject to extensive first pass metabolism consisting chiefly of conjugation with sulfate in the gut wall. Both EE_2 and progestogens are well absorbed in patients with an ileostomy or with diseases such as cystic fibrosis or Crohn's disease. However in patients with celiac disease (gluten-sensitive enteropathy) the gut wall is less able to conjugate EE_2 and thus its bioavailability is increased. The bioavailability returns to control values as the disease is improved following gluten withdrawal. Other drugs that are conjugated with sulfate, such as vitamin C and paracetamol, compete for available sulfate when coadministered with OCS leading to high plasma levels of EE_2.

Enzyme-inducing agents such as rifampicin, phenobarbitone, phenytoin and carbamazepine reduce blood levels of the OCS leading to contraceptive failure. In the case of anticonvulsants (but not rifampicin) this can be easily overcome by increasing the dose of OCS used. Broad-spectrum antibiotics are reported to cause failure of contraception by interfering with the enterohepatic circulation of EE_2 but limited systematic studies show no evidence of such an interaction. Nevertheless practitioners are advised to recommend the use of alternative contraceptive precautions for women receiving broad-spectrum antibiotics concurrently with their OCS preparation.

Introduction

Oral contraceptive steroids (OCS) have been in widespread use for more than 30 years. However, it is only in the last ten years that information has become available concerning the pharmacokinetics of these drugs. This has come about because of the

development of sensitive and specific assays, mostly based on radioimmunoassay procedures [1–3]. Thus ethinylestradiol (EE_2) can now be reliably detected in plasma down to 10–20 pg/ml and this has enabled us to measure the kinetics of contraceptive steroids with some accuracy.

Pharmacokinetics of contraceptive steroids

The progestogens are all well absorbed following oral administration. Levonorgestrel shows a near 100% bioavailability [2] while norethisterone is subject to a slight first-pass effect with an average bioavailability of 80% [3]. Desogestrel, a widely used and recently introduced gestagen, is inactive as such and is extensively oxidized in the liver to its active metabolite, 3-keto desogestrel. Thus, it is perhaps not surprising that the mean bioavailability of desogestrel measured as 3-keto desogestrel is less than 100% [4], although the mean figure is about 70–80%. Ethinylestradiol, in contrast, is poorly bioavailable, not because of poor absorption but because of extensive first-pass metabolism. Ethinylestradiol has a mean bioavailability of about 40–50% [1] but there is a considerable inter-individual variation, with figures varying from 10–75% [1]. The first-pass metabolism of EE_2 is partly due to hydroxylation in the liver but mostly it is due to conjugation processes occurring in the gut wall. *In vitro* experiments with human intestinal biopsies showed that gut mucosa is capable of extensive sulfation of EE_2 [5] and studies *in vivo* in patients with a catheter in their hepatic portal vein showed that 60% of the first-pass metabolism of EE_2 is caused by gut wall sulfation [6]. This metabolic route, while relatively unusual, is of clinical importance since the supply of available sulfate is limited. Other drugs which are also metabolized by sulfation may compete for the sulfate. Thus, less EE_2 will be sulfated leading to greater absorption of unchanged EE_2, with potentially toxic effects. Thus, ascorbic acid [7] and paracetamol [8] both lead to increased EE_2 blood levels when coadministered with combined contraceptive steroid preparations. Any potential adverse effects can be avoided by making sure that the two drugs are given at least two hours apart.

Effect of disease on kinetics of contraceptive steroids

The kinetics of the progestogens seem to be affected very little by disease processes likely to be found in women taking the contraceptive preparations. However, ethinylestradiol, because of its extensive gut wall metabolism, may be affected by diseases that affect the gut wall. Initial studies *in vitro* suggested that gut mucosa taken from patients with celiac disease was relatively poor at conjugating EE_2 compared with normal mucosa. This was confirmed in a more extensive examination and, as expected, in the *in vivo* studies, the bioavailability of EE_2 was significantly increased in patients with celiac disease [9]. Following treatment with a gluten-free diet, the bioavailability of EE_2 returned towards normal values. The bioavailability of EE_2 and of progestogens is not impaired in women with an ileostomy [10], or with

cystic fibrosis [11]. There is no evidence about the effect of diarrhea *per se* on the absorption of the contraceptive steroids, but from the evidence given above it would seem unlikely that the absorption would be affected except by the most severe forms of diarrhea. Our study involving portal vein catheterization showed that the rate of absorption of EE_2 is usually very rapid.

Drug interactions with oral contraceptive steroids

Rifampicin

Rifampicin is known to be a potent enzyme-inducing agent both in animals and in man [12]. The effect on drug-metabolizing enzymes may be noted after only two days' therapy with rifampicin. Rifampicin seems to be a particularly potent enzyme-inducing agent and, in our studies in women taking oral contraceptive steroids, a four- or five-fold change in the rate of drug metabolism was sometimes seen. Rifampicin increases the rate of metabolic destruction of both EE_2 [13] and progestogens [14] such as norethisterone. Although the amount of change seen following rifampicin may be great, there is also considerable interindividual variation in the response seen. Since rifampicin is used for the treatment of tuberculosis in relatively short courses, it is unlikely that contraceptive efficacy can be achieved with the OCS and it is recommended that alternative methods of contraception are used in women taking rifampicin. One month after stopping rifampicin, it is likely that the enzyme-inducing effects will have worn off and standard doses of OCS should be effective. Women taking rifampicin for treatment of nasal carriage of *Neisseria meningitidis* should note that their oral contraceptive steroid may lose its efficacy. They should use alternative contraceptive precautions while taking rifampicin and for the next four weeks.

Anticonvulsants

Anticonvulsant drugs such as phenobarbitone, phenytoin and carbamazepine are all enzyme-inducing agents [12]. There is debate over which is the most potent enzyme inducer and it is likely that this is a sterile argument since they probably affect different P450 isozymes [15]. Coulam and Annegers [16] showed clearly that all 3 anticonvulsants could cause failure of contraception in women taking OCS and, in a review of cases reported to the Committee on Safety of Medicines (CSM) over a 17-year period, Back *et al.* [17] found that phenytoin was reported most commonly to cause failure of contraception in women taking OCS. A total of 25 cases of contraceptive failure were reported in women taking phenytoin compared with 20 in women taking phenobarbitone and 6 in women taking carbamazepine. Phenobarbitone (30 mg bd), when given in controlled study to women taking OCS, produced a fall in the plasma concentration of EE_2 [18]. In two of the four women studied, the fall in EE_2 levels was substantial and associated with breakthrough

bleeding. In women taking phenytoin and carbamazepine [19], both drugs caused a reduction in the area under the plasma concentration versus time curve (AUC) of both EE_2 and levonorgestrel in women given a single dose of the steroids before and during anticonvulsant drug therapy. On average, there was a 50% reduction in the AUC values and this degree of change would be expected to have pharmacodynamic implications during long-term therapy. It is no longer necessary for patients on phenytoin, carbamazepine or phenobarbitone to use alternative contraceptive precautions, since contraceptive control can be obtained by increasing the dose of the OCS preparation. Thus we start such women on a 50 μg EE_2 preparation and increase the dose to 80 μg or even 100 μg EE_2 daily if breakthrough bleeding still occurs. The increased metabolism of EE_2 and progestogen will produce larger amounts of metabolites, but these are not thought to have any pharmacological activity. As an alternative, anticonvulsant therapy with sodium valproate may be used since this drug does not interfere with oral contraceptive steroid therapy [20].

Broad-spectrum antibiotics

Broad-spectrum antibiotics have been reported to interfere with the actions of OCS for many years. The first report of this interaction causing contraceptive failure was in 1975 [21] and there has been a steady trickle of such reports since then. Back *et al.* [17] reviewed all such reports to the CSM over a 17-year period (1968–1984) and found 63 reports of contraceptive failure following the use of broad-spectrum antibiotics. The majority of these reports involved penicillins, particularly ampicillin and amoxycillin, although other antibiotics such as cotrimoxazole were implicated.

Ethinylestradiol, following its absorption, is conjugated both with sulfate and in the liver with glucuronic acid. These conjugates are then excreted in the bile and return to the gastrointestinal tract. In the colon, these EE_2 conjugates are split by bacteria – mostly *Clostridia* spp. – to release the unchanged EE_2 which can then be reabsorbed. This enterohepatic recirculation of EE_2 can be interrupted, at least in theory, by broad-spectrum antibiotics which kill off the bacteria involved in the deconjugation process. How important the enterohepatic recirculation is for the maintenance of plasma levels of EE_2 is uncertain. There is little doubt that in animal studies (e.g. rat) the enterohepatic recirculation of EE_2 is notable and its interruption by antibiotics is important [22,23]. However, in women, studies in patients with an ileostomy do not reveal a major role for enterohepatic recirculation [10]. Equally, formal clinical trials with ampicillin [24–26] show no change in blood levels of EE_2 when ampicillin is given with the OCS preparation. Studies with tetracycline and erythromycin likewise give no support for an antibiotic interaction [27]. Cotrimoxazole, which appears in the CSM reports as a cause of contraceptive failure [17], when studied in a formal trial, significantly increased the blood levels of EE_2 and this was accompanied by a significantly enhanced pharmacodynamic effect, as shown by further suppression of FSH levels [28].

We feel that there is no scientific evidence in favor of a systematic interaction between broad-spectrum antibiotics and OCS. Nevertheless, the attention given to

this subject in drug data sheets and the CSM data make it difficult to claim that all reports are due to a missed pill. There may be individuals especially at risk of this interaction, in particular, women who are unable to hydroxylate EE_2 and thus excrete their EE_2 as direct conjugates of EE_2 [29]. It is impossible to estimate how common such women might be in the community. Thus it is safer to recommend the use of alternative contraceptive precautions to women taking broad-spectrum antibiotics with their OCS. These precautions should continue for 7 days after the antibiotic has been stopped. Alternatively, cotrimoxazole can be given (provided the microbiological indications are correct) without using alternative contraceptive precautions, because of its effect of increasing EE_2 plasma concentrations.

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Resumé

Les contraceptifs oraux stéroïdes (OCS) sont bien absorbés par l'appareil gastro-intestinal humain. Toutefois, si les progestogènes sont presque entièrement biodisponibles, l'éthinyl oestradiol (EE_2) doit passer par un premier métabolisme important qui consiste essentiellement en une conjugaison au sulfate dans la paroi de l'intestin. Aussi bien le EE_2 que les progestogènes sont bien absorbés chez des patientes ayant une iléostomie ou souffrant de maladies telles que la fibrose kystique ou la maladie de Crohn. Cependant, chez les patientes souffrant de maladie coeliaque (entéropathie d'intolérance au gluten), la paroi intestinale est moins à même de conjuguer l'EE_2, de sorte que la biodisponibilité est accrue. La biodisponibilité reprend des valeurs normales lorsque le gluten est éliminé. D'autres substances qui se conjuguent avec le sulfate, telles que la vitamine C et le paracétamol se font concurrence pour le sulfate disponible lorsqu'elles sont administrées en même temps que les OCS, entraînant des niveaux plasmatiques élevés de EE_2.

Les agents inducteurs d'enzymes, tels que la rifampicine, le phénobarbital, la phénytoïne et la carbamazépine, réduisent les niveaux sanguins des OCS, entraînant l'échec du contraceptif. Dans le cas des anticonvulsifs (mais non de la rifampicine) ce phénomène peut facilement être surmonté en augmentant la dose de OCS administrée. On a rapporté que les antibiotiques à large spectre provoquent l'échec de la contraception du fait qu'ils compromettent la circulation entéro-hépatique du EE_2, mais certaines études systématiques limitées n'ont pas fait ressortir cette interaction. Néanmoins, il est

conseillé aux praticiens de recommander d'autres précautions anticonceptionnelles aux femmes qui reçoivent, en même temps qu'un contraceptif oral stéroïde, un traitement aux antibiotiques à large spectre.

Resumen

Los anticonceptivos orales esteroides (AOE) son bien absorbidos por el aparato gastrointestinal humano. No obstante, si bien los progestágenos son casi totalmente biodisponibles, el etinilestradiol (EE_2) debe pasar por un primer metabolismo importante que consiste esencialmente en una conjugación con sulfato en la pared intestinal. Tanto el EE_2 como los progestágenos son bien absorbidos en las pacientes con una ileostomía o afectadas de enfermedades como fibrosis quística o la enfermedad de Crohn. Sin embargo, en pacientes con enfermedad celíaca (enteropatía de intolerancia al gluten), la pared intestinal en menos capaz de conjugar el EE_2, de modo que la biodisponibilidad aumenta. La biodisponibilidad retoma valores normales cuando el gluten es eliminado. Otras sustancias que se conjugan con el sulfato, como la vitamina C y el paracetamol, compiten por el sulfato disponible cuando son administradas al mismo tiempo que los AOE, ocasionando niveles plasmáticos elevados de EE_2.

Los agentes inductores de enzimas, como la rifampicina, el fenobarbital, la fenitoína y la carbamazepina, reducen los niveles sanguíneos de los AOE, provocando el fracaso de los anticonceptivos. En el caso de los anticonvulsivos (pero no de la rifampicina), este fenómeno puede ser fácilmente superado al aumentarse la dosis de AOE utilizada. Se ha informado de que los antibióticos de amplio espectro provocan el fracaso de la anticoncepción porque interfieren con la circulación entero-hepática del EE_2, pero algunos estudios sistemáticos limitados no indican tal interacción. Sin embargo, se aconseja a los practicantes recomendar otras precauciones anticonceptivas a las mujeres que reciben antibióticos de amplio espectro juntamente con AOE.