DRUG INTERACTION INVOLVING ORAL CONTRACEPTIVES

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ABSTRACT

Metabolism of contraceptive compounds may be influenced by various drugs. Of clinical importance is induction by barbiturates, by diphenylhydantoin, and especially by rifampicin, of enzymes that are responsible for degradation of estrogens. The major target is the hepatic microsomal estrogen-2-hydroxylase. Another type of interaction of drugs with disposition and effectiveness of estrogens is impairment of their enterohepatic circulation. This may be due to absorbtion of biliary estrogen conjugates (by cholestyramine) or to insufficient cleavage of the conjugate by intestinal bacteria, the latter being observed after administration of antibiotics (ampicillin, neomycin).

INTRODUCTION

Three different regimens of oral contraception are currently used: "combination pills" and "sequential medication" include both estrogenic and progestational components while the "minipill" only contains a gestagen. The effectiveness of contraception depends on unimpaired activity and action of these two classes of female sex steroids. Therefore, when dealing with metabolic interaction of drugs with oral contraceptives, the metabolic fates of synthetic estrogens and of synthetic gestagens must be considered. As metabolism of contraceptive steroids is the subject of some recent reviews /1-3/, only those aspects will be mentioned here which are pertinent to drug interaction.

Major pathways of metabolism of synthetic *gestagens* are reductive and include ring A of the steroid. Hydroxylated metabolites usually occur to a much lesser extent. Fig. 1 shows the metabolism in man of one of the most widely used synthetic gestagens, norethisterone /1, 4/. Also the synthetic gestagens of the 17α-hydroxyprogesterone series are mainly metabolised *via* ring-A-reduction /1/. By contrast, some animal experiments /5/ show that after barbiturate induction a major metabolite of the synthetic 17α-hydroxyprogesterone gestagen chlormadinone acetate is the hydroxylation product 2α-hydroxy-chlormadinone acetate. This may be indicative of possible preponderance of hydroxylative pathways after induction of hydroxylating enzymes, but unfortunately more information on possible drug interactions involving progestational compounds at the level of metabolism is lacking.

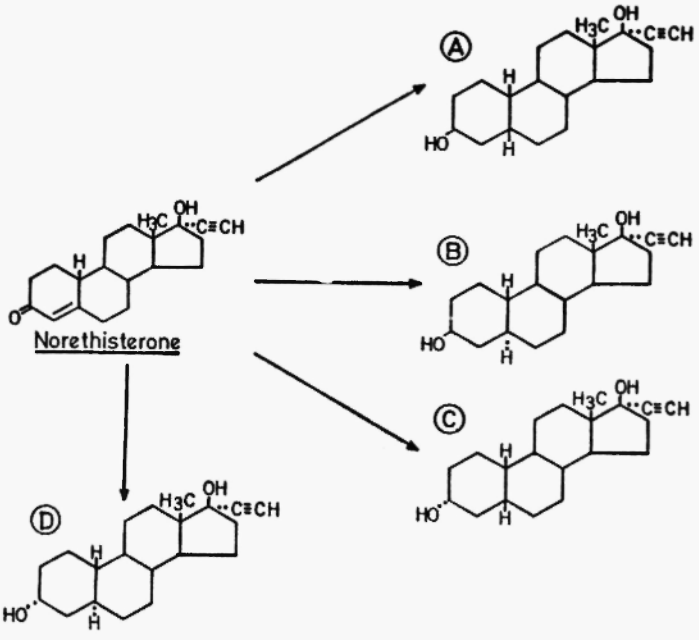

Fig. 1. Metabolism of norethisterone (norethindrone) in man (1, 4). Metabolites obtained by reduction of ring A:

A: 17α-ethynyl-19-nor-5α-androstane-3α, 17β-diol;

B: 17α-ethynyl-19-nor-5β-androstane-3α, 17β-diol;

C: 17α-ethynyl-19-nor-5α-androstane-3β, 17β-diol;

D: 17α-ethynyl-19-nor-5β-androstane-3β, 17β-diol.

Much better is the knowledge about metabolism of synthetic *estrogens* and about drug effects on the latter. Two estrogenic compounds are currently used for oral contraception, 17α-ethynylestradiol and its 3-methyl ether, mestranol (Fig. 2). In man, about half of a mestranol dose is transformed into the hormonally active ethynylestradiol /6/. Fig. 2 also summarises the metabolic routes involved in conversion of ethynylestradiol and mestranol. The major pathway /3/

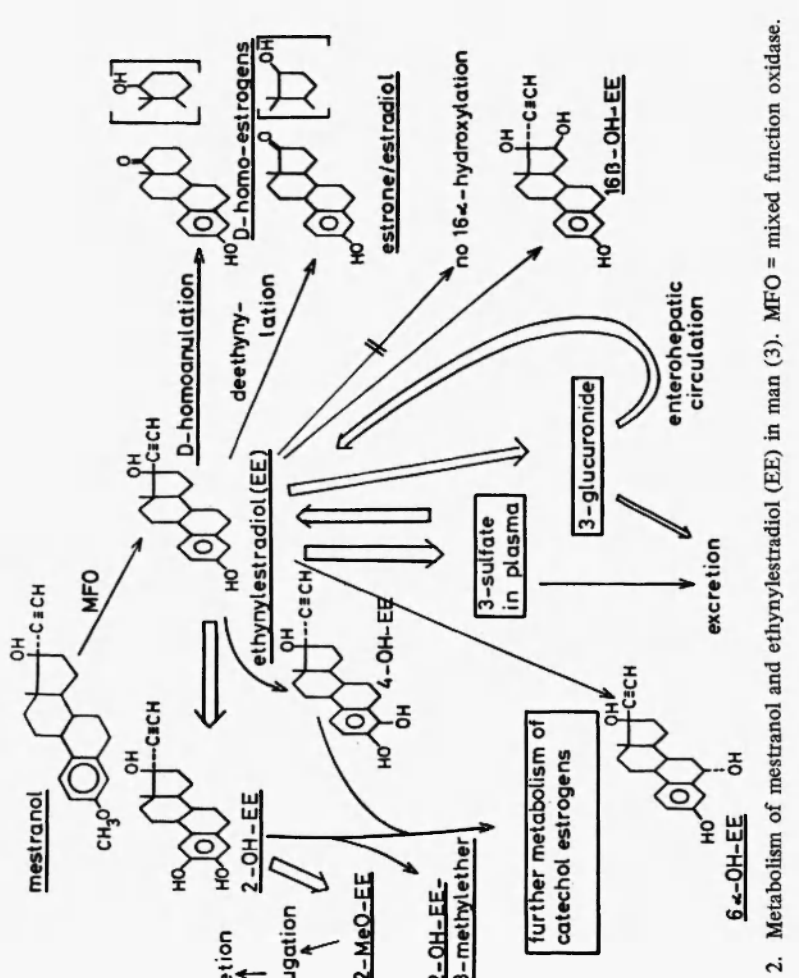

Fig. 2. Metabolism of mestranol and ethynylestradiol (EE) in man (3). MFO = mixed function oxidase.

is aromatic hydroxylation at C-2 (to a lesser degree also at C-4). In man, an average of 30% of ingested ethynylestradiol is ortho-hydroxylated (at C-2 / C-4; 7). Another pathway is de-ethynylation /2,8-10/: de-ethynylated metabolites are reported /9/ to comprise 15-20% of the total glucuronide metabolites of ethynylestradiol in urine. The initial step of de-ethynylation probably is oxygenation of the ethynyl triple bond by a microsomal monooxygenase /10/. Other possible pathways of metabolism of ethynylestradiol are hydroxylations at ring B (C-6) or at the 16β-position of ring D (see Fig. 2 and Ref. 3).

Compounds which interact with these estrogen hydroxylations have a potential effect on the biological activity of synthetic estrogens.

INDUCTION OF HYDROXYLATING ENZYMES

The "prototype" of an inducer of oxidative drug metabolism, *phenobarbital,* has been found to decrease the uterotrophic action of ethynylestradiol, mestranol and diethylstilbestrol in rats /11/. Barbiturates enhance ring-B-hydroxylation of ethynylestradiol in man /12/, but as this metabolic route is only a minor one, its biological significance is limited. However, rat experiments /13/ have shown that phenobarbital also stimulates aromatic hydroxylation of ethynylestradiol in rats.

Hempel and coworkers /14/ studied 51 patients receiving oral contraceptives of the combination type and different amounts of phenobarbital. Thirty patients showed spottings and/or breakthrough bleedings indicating insufficient effectivity of the estrogenic component of the contraceptive; one patient became pregnant. This, along with the data of the animal experiments, very much indicates that increased breakdown of steroid contraceptives occurs in man after phenobarbital administration. This is especially important in epileptic patients where barbiturates or barbiturate analogs are prescribed for long-term treatment.

Diphenylhydantoin (Dilantin, Phenytoin) which often is combined with these drugs in the management of epilepsy may also enhance aromatic hydroxylation of estrogens in some strains of rats /15/. When studying 25 cases of "pill failure", Hempel *et al.* /14/ detected 4 patients under anti-epileptic therapy. Also, Janz and Schmidt /16/ reported that 3 patients became pregnant while taking antiepileptics (primidone, phenobarbital, diphenylhydantoin) and oral contraceptives of the combination type. A similar case has been reported by Nenyon /17/.

It also has been claimed /14/ that administration of some analgesics together with oral contraceptives should result in increased rate of breakthrough bleedings; however, the validity of these data has not been confirmed.

By far the most potent inducer of estrogen metabolising enzymes in man is the antituberculous drug *rifampicin.* Rifampicin is also known to interfere with the effectiveness of several other drugs including anticoagulants /18,19/, tolbutamide /20-22/, cardiac glycosides /23/ and barbiturates /21,22/.

Reimers and Jezek /24/ reported in 1971 that simultaneous administration of rifampicin and oral contraceptives resulted in increased incidence of spottings and breakthrough bleedings. According to a study by Nocke-Finck, Breuer and Reimers /25/ five pregnancies occurred in 88 patients treated with rifampicin and oral contraceptives. The authors suggested that this effect may be due to enzyme induction /26/.

Subsequently, several other reports also showed a diminished antifertility effect of oral contraceptives, if the patients were under treatment with rifampicin /27-30/.

In 1973, Remmer, Schoene and Fleischmann /31,32/ demonstrated that rifampicin causes induction of drug metabolising enzymes in the endoplasmic reticulum of human liver. Obviously, there are marked species differences in inductive response to rifampicin: administration of the compound to mice increases hepatic cytochrome P-450, NADPH-cytochrome-c-reductase and hydroxylation of drugs /33,34/ while in rats, only NADPH-cytochrome-c-reductase increases /35,36/. When patients are treated with the usual therapeutic dose of 600 mg/day rifampicin for 6-10 days, hepatic microsomal cytochrome P-450 increases 2-3 fold /31,37/. Liver microsomes from patients treated with rifampicin also show an, about fourfold, increase in their ability to ortho-hydroxylate estradiol and ethynylestradiol, compared to those from untreated normal subjects /37/. It has already been mentioned above that aromatic hydroxylation is the major pathway in the metabolism of estrogens.

Further studies /7/ examined the influence of rifampicin treatment on the pharmacokinetics of ethynylestradiol. Ethynylestradiol, when given to humans, shows a biphasic plasma decline with a $t_{1/2}$ of 7.5±1.7 (S.D.) hours in the second (β) phase. Administration of rifampicin (600 mg daily for 6 days) shifts this half-life to 3.3±0.9 hours while

the apparent volume of distribution is not changed (Fig. 3). Moreover, the rate of aromatic hydroxylation in man has been determined using [2,4,6,7-^{3}H] labelled ethynylestradiol. After administration of this compound, determination of the tritiated water (H^3HO) formed provides a sensitive tool to follow aromatic hydroxylation. The initial rate of oxidation of [2,4,6,7-^{3}H-] ethynylestradiol is increased more than twofold by rifampicin treatment /7/. The data which have been elaborated in man therefore show that rifampicin induces the estrogen-2-hydroxylase in the endoplasmic reticulum of human liver, and explains the reduced effectiveness of estrogens in contraceptives, if the patients are treated with rifampicin.

Endogenous hormones may respond to enhanced breakdown with an increase of their secretion rate so that changes due to enzyme induction become even more complex. This view is supported by the observation of Edwards *et al.* /38/ that secretion of cortisol is increased in patients treated with rifampicin. In guinea pigs /39/ and in man /40/ rifampicin also induces an enzyme responsible for 6β-hydroxylation of cortisol. This suggests that induction by rifampicin ought not to be limited to drug metabolising or estrogen metabolising enzymes, but may also be of importance for metabolism of neutral steroid hormones, possibly including gestagens. It is also of interest that rifampicin treatment apparently increases oxidative metabolism of some synthetic glucocorticoids, e.g. methylprednisolone /41/.

INHIBITION OF HYDROXYLATING ENZYMES AND ROLE OF LIVER DAMAGE

Inhibition of metabolism of contraceptive steroids by drugs or xenobiotics is not of clinical significance. Experimentally, SKF 525 A has a moderate inhibitory effect on hepatic microsomal aromatic hydroxylation of natural and synthetic estrogens /13/. A much stronger inhibitory effect has been reported to be due to some novel compounds of the 1.2.3 - benzothiadiazole and arylimidazole classes which were originally designed as insecticide synergists /42/. The most potent inhibitor, 1-naphthyl-4-/5/-imidazole, inhibited aromatic hydroxylation of ethynylestradiol by a $\bar{K}_i$ of 3×10^{-6} M. Hence, the estrogen-inactivating system may be susceptible to inhibition by possible environmental pollutants like insecticide synergists.

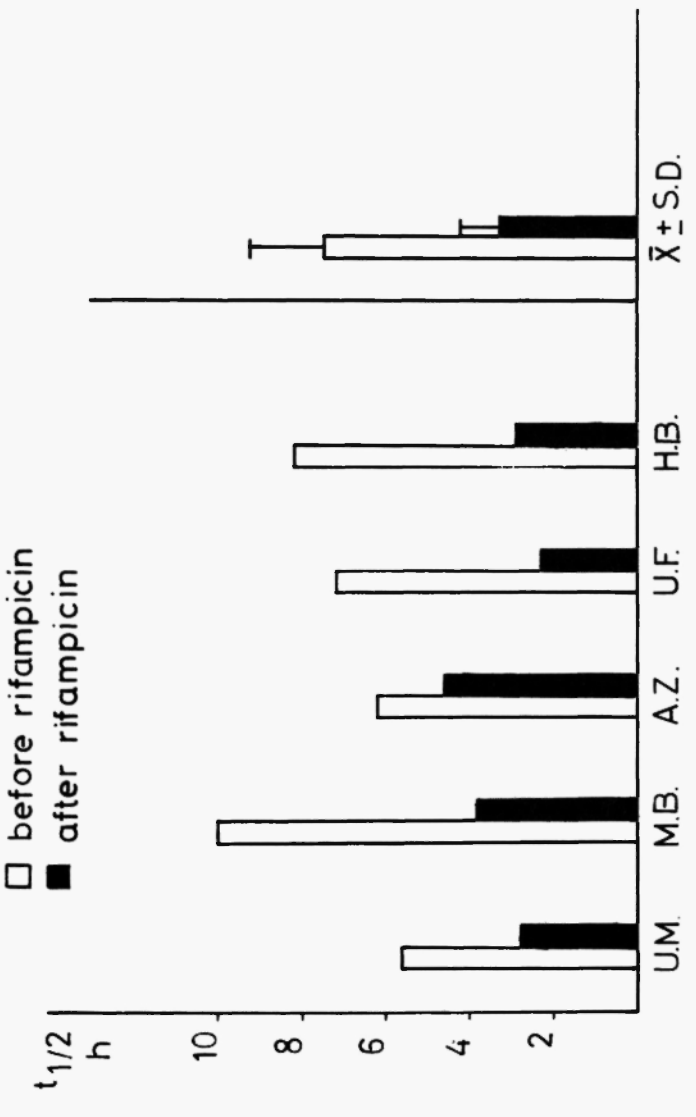

Fig. 3. Half-life (β-phase) of intravenous ethynylestradiol in man before and after administration of rifampicin (see Ref. 7).

With regard to endogenous estrogenic hormones, the effect of liver damage on estrogen metabolism is of considerable clinical importance /3/ as one of the symptoms seen in men suffering from hepatic cirrhosis is gynecomastia /43,44/. Zumoff *et al.* /45/ observed a decrease of 2-hydroxylation of endogenous estrogens in patients with liver cirrhosis along with an increase of 16α-hydroxylation. The same is observed in rats with thioacetamide-induced liver fibrosis /46,47/. The primary lesion seems to be destruction of the specific cytochrome P-450 species which catalyses 2-hydroxylation of estrogens /48/. Although experimentally 2-hydroxylation of ethynylestradiol is also impaired in liver damage, this effect on metabolism of synthetic sex steroids is only of theoretical interest and has no clinical implications.

EFFECT OF DRUGS ON ENTEROHEPATIC CIRCULATION OF ESTROGENS

It has been recognized by Sandberg and Slaunwhite /49/ in 1957 that enterohepatic circulation is of quantitative importance for disposition of estrogens in man. This contrasts to the patterns of the other, "neutral" steroid hormones /50/. Changes in metabolism of natural estrogens after application of *ampicillin* have been explained by interference with the enterohepatic circulation of estrogens /51/. Recent animal studies /52/ are supportive of this view: the antibiotic *neomycin,* when orally applied to rats, markedly inhibits enterohepatic re-circulation of metabolites of estradiol and mestranol by directly affecting the gut microflora which is responsible for de-conjugation of the biliary steroid conjugates.

Interference of antibiotics with enterohepatic circulation of synthetic estrogens can be assumed to be of clinical importance since 3 women became pregnant while taking oral contraceptives together with *ampicillin* /53/.

Another drug which may interfere with enterohepatic circulation of estrogens is *cholestyramine* which is prescribed in order to prevent bile acid conjugates undergoing enterohepatic circulation. This anion exchange polystyrene resin also apparently binds other biliary steroid conjugates. It could recently be demonstrated /54/ that the plasma half-life of ethynylestradiol in the β phase, which depends on the rate of metabolism of ethynylestradiol /7/, is shortened by administration of cholestyramine.

In a normal subject which was studied, the $t_{1/2}$ β of ethynylestradiol, normally 8.2 h, was reduced to 4.8 h under p.o. administration of 3 x 4 g/day cholestyramine. The apparent volume of distribution was unchanged. Along with the present data on impairment of enterohepatic circulation by antibiotics (see above) this effect of cholestyramine could be interpreted in a way that cholestyramine increases elimination of ethynylestradiol by preventing it from enterohepatic re-circulation.

CONCLUDING REMARKS

While metabolism and efficacy of oral contraceptives may be definitely influenced by a series of other drugs, alteration by contraceptive compounds of other drugs' metabolism is questionable and not of apparent clinical relevance /55/. This must be viewed along with the low doses of estrogens and gestagens used for oral contraception today /56/. Pincus /57/, in his classical studies on oral contraception, has used as the estrogenic component 150 μg mestranol and a high gestagen dose. Now, the recommended daily dose of estrogen in contraceptive formulations is 50 μg ethynylestradiol /58-60/ or even less /61/. Thromboembolic side effects of oral contraceptives are mainly dependent on the dose of estrogen prescribed; a low dose of estrogen decreases the incidence of such adverse reactions. However, at a lower dose range factors which enhance metabolic elimination and thereby decrease the hormonal effectiveness become even more important /62/. Such factors include induction of estrogen metabolising enzymes, mainly the estrogen-2-hydroxylase, and interference of drugs with the enterohepatic circulation of estrogens. Decreased effectiveness of the estrogenic component of oral contraceptives results in spottings, breakthrough bleedings and "pill failure". This must be considered when treating a patient taking oral contraceptives with inducing agents (barbiturates, diphenylhydantoin, and especially rifampicin) or with agents that interfere with enterohepatic circulation of estrogens (antibiotics like ampicillin and neomycin; cholestyramine).

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