Interactions between Clinically Used Drugs and Oral Contraceptives

Hermann M. Bolt
Institut fur Arbeitsphysiologie an der Universität Dortmund, Germany

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 (cytochrome P450 3A4). Another type of interaction of drugs with disposition and effectiveness of estrogens is impairment of their enterohepatic circulation. This may be due to absorption of biliary estrogen conjugates (e.g., by cholestyramine) or to insufficient cleavage of the conjugate by intestinal bacteria, the latter being observed after administration of antibiotics (e.g., ampicillin, neomycin). — Environ Health Perspect 102(Suppl 9):35–38 (1994)

Key words: oral contraceptives, ethinylestradiol, mestranol, rifampicin, barbiturates, antiepileptics, antibiotics, insecticide synergists

Introduction

The effectiveness of oral contraception depends on unimpaired action and activity of synthetic estrogens and gestagens. As metabolism of contraceptive steroids is the subject of reviews (1–3), only those aspects which are pertinent to drug interaction will be mentioned here.

Major pathways of metabolism of synthetic gestagens are reductive and include ring A of the steroid (4). Hydroxylated metabolites usually occur to a lesser extent. By contrast, some animal experiments (5) show that after barbiturate induction a major metabolite of a synthetic gestagen (chlormadinone acetate) is the 2-hydroxylation product (2α-hydroxychlormadinone acetate). This may be indicative of possible preponderance of hydroxylative pathways after induction of hydroxylating enzymes.

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, 17-α-ethinylestradiol and its 3-methyl ether, mestranol. In humans, about half of a mestranol dose is transformed into the hormonally active ethinylestradiol (6). The major pathway of ethinylestradiol metabolism (2,3) is aromatic hydroxylation at C-2 (to a lesser degree also at C-4), mainly by cytochrome P450 3A4. In humans, an average of 30% of ingested ethinylestradiol is α-hydroxylated (at C-2/C-4; 7). Another pathway is deethinylation (1,8–10). Deethinylated metabolites are reported (9) to comprise 15 to 20% of the total glucuronide metabolites of ethinylestradiol in urine. The initial step of de-ethinylation probably is oxygenation of the ethinyl triple bond by a microsomal monoxygenase (10). Other possible pathways of metabolism of ethinylestradiol are hydroxylations at ring B (C-6) or at the 16β-position of ring D (2).

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

Induction of Hydroxylating Enzymes

The “prototype” of an inducer of oxidative drug metabolism, phenobarbital, has been found to decrease the urotropitic action of ethinylestradiol, mestranol and diethylstilbestrol in rats (11). Barbiturates enhance ring-B-hydroxylation of ethinylestradiol 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 ethinylestradiol in rats.

Hempel and co-workers (14) have studied 51 patients receiving oral contraceptives of the combination type and different amounts of phenobarbital. Thirty patients showed spotting and/or breakthrough bleedings indicating insufficient effectiveness 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 and/or related compounds are prescribed for long-term treatment.

Diphenylhydantoin 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) found four patients among those who were under antiepileptic therapy. Also, Janz and Schmidt (16) reported that three patients became pregnant while taking antiepileptics (primidone, phenobarbital, and 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 not been confirmed.

By far, the most potent inducer of estrogen-metabolizing 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), tolbutamides (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 spotting and breakthrough bleedings. According to a study by Nocks-Fink et al. (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).
In 1973, Remmer et al. (31,32) demonstrated that rifampicin causes induction of drug metabolism 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 P450, 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 60 mg/day rifampicin for 6 to 10 days, hepatic microsomal cytochrome P450 increases 2- to 3-fold (37,38). Later, it has been found that rifampicin especially induces human liver cytochrome P450 3A4 (3). Liver microsomes from patients treated with rifampicin also show about a 4-fold increase in their ability to α-hydroxylate estradiol and ethinylestradiol, 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 synthetic estrogens.

Further studies (7) examined the influence of rifampicin treatment on the pharmacokinetics of ethinylestradiol. Ethinylestradiol, when given to humans, showed a biphasic plasma t1/2 of 7.5 ± 1.7 SD hr in the second (β) phase. Administration of rifampicin (600 mg daily for 6 days) shifted this half-life to 3.3 ± 0.9 hr while the apparent volume of distribution was not changed. Moreover, the rate of aromatic hydroxylation in man has been determined using (2,4,6,7-3H) labeled ethinylestradiol. After administration of this compound, determination of the tritiated water (H3HO) formed provides a sensitive tool to follow aromatic hydroxylation. The initial rate of oxidation of (2,4,6,7-3H)-ethinylestradiol is increased more than 2-fold 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 explain the markedly 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 confirmed 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 6-β-hydroxylation of cortisol. It is also of interest that rifampicin treatment apparently increases oxidative metabolism of some synthetic glucocorticoids, e.g., methylprednisolone (41).

Inhibition of Hydroxyrating Enzymes and Role of Liver Damage

Experimentally, SKF 525A 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 compounds of the 1,2,2-benzothiaziazoyle and arylimidazole classes which were designed as insecticide synergists (42). The most potent inhibitor of this class, 1-naphthyl(45)-imidazole, inhibited aromatic hydroxylation of ethinylestradiol by a KI of 3 x 10-6M. Hence, the estrogen-inactivating system may be susceptible to inhibition by possible environmental pollutants such as insecticide synergists.

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 man suffering from hepatic cirrhosis is gynecomastia (43,44). Zumoff et al. (45) have observed a decrease of 2-hydroxylation of endogenous estrogens in patients with liver cirrhosis along with an increase of 16-α-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 P450 species that catalyzes 2-hydroxylation of estrogens (48).

Experimentally 2-hydroxylation of ethinylestradiol is also impaired in liver damage; this effect of synthetic sex steroids on metabolism is only of theoretical interest and has no clinical implications.

Effect of Drugs on Enterohelial Circulation of Estrogens

It has been recognized by Sandberg and Slawnowile (49) in 1957 that enterohelial 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 enterohelial circulation of estrogens (51). Recent animal studies (52) are supportive of this view: the antibiotic neomycin, when orally applied to rats, markedly inhibits enterohelial recirculation of metabolites of estradiol and mestranol by directly affecting the gut microflora which is responsible for deconjugation of the biliary steroid conjugates.

Interference of antibiotics with enterohelial circulation of synthetic estrogens can be assumed to be of clinical importance since three women became pregnant while taking oral contraceptives together with ampicillin (53).

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

In a normal subject which was studied, the t1/2 β of ethinylestradiol, normally 8.2 hr, was reduced to 4.8 hr under administration of 3 x 4 g/day cholestyramine. The apparent volume of distribution was unchanged. Along with the present data on impairment of enterohelial circulation by antibiotics, this effect of cholestyramine could be interpreted in a way that cholestyramine increases elimination of ethinylestradiol by preventing it from enterohelial recirculation.

Conclusion

While metabolism and efficacy of oral contraceptives are influenced by a series of other drugs, alteration by contraceptive compounds of other drugs' metabolism is questionable (54). This must be viewed along with the low doses of estrogens and gestagens used for oral contraception (55). Pincus (56), 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 ethinylestradiol or less (57–59). 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 (60). Such factors include induction of estrogen metabolizing 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 spotting, breakthrough bleedings and "pill failure."

REFERENCES

1. Helton ED, Goldzieher JW. Metabolism of ethynyl estrogens. J Toxicol Environ Health 3:231 (1977).
2. Bolt HM. Metabolism of estrogens: natural and synthetic. Pharmacol Ther 4:155 (1979).
3. Guengerich FP. Inhibition of oral contraceptive steroid-metabolizing enzymes by steroids and drugs. Am J Obstet Gynecol 1:3-2159-2163 (1990).
4. Braselton WE, Lin TJ, Mills TM, Ellegod JO, Mahesh VB. Identification and measurement by gas chromatography-mass spectrometry of norethindrone and metabolites in human urine and blood. J Steroid Biochem 8:9 (1977).
5. Hendy RW, Palmer KH, Wall ME, Plantadosi C. The metabolism of antifertility steroids: The in vitro metabolism of chlormadinone acetate. Drug Metab Dispos 2:214 (1974).
6. Bolt HM, Bolt WH. Pharmacokinetics of mestranol in relation to its oestrogenic activity. Eur J Clin Pharmacol 7:295 (1974).
7. Bolt HM, Bolt M, Kappus H. Interaction of rifampicin treatment with pharmacokinetics and metabolism of ethynloestriadiol in man. Acta Endocrinol 85:189 (1977).
8. Kulkarni BD, Goldzieher JW. A preliminary report on urinary excretion pattern and method of isolation of 14C-ethynylestradiol metabolites in women. Contraception 1:47 (1970).
9. Williams MC, Helton ED, Goldzieher JW. The urinary metabolites of 17-alpha-ethynylestradiol in women. Steroids 25:229 (1975).
10. Guengerich FP. Mechanism-based inactivation of human liver microsomal cytochrome P-450 III A4 by gestodene. Chem Res Toxicol 3:363-371 (1990).
11. Levin W, Welch RM, Conney AH. Decreased uterotropic potency of oral contraceptives in rats pretreated with phenobarbital. Endocrinology 83:149 (1968).
12. Wenzel M, Stahl HJ. Verstärkte Hydroxylierung von Östrogene zwischen den Menschen nach Arzneimittelgabe. Hoppe-Seyler's Z Physiol Chem 351:761 (1970).
13. Bolt HM, Kappus H, Remmer H. Studies on the metabolism of ethynylestradiol in vitro and in vivo. The significance of 2-hydroxylolation and the formation of polar products. Xenobiotica 3:773 (1973).
14. Hempel E, Bohm W, Carol W, and Klinger G. Medikamentös Enzyminduktion und hormonale Kontrazeption. Zbl Gynaek 95:1151 (1973).
15. Hauser RE. Beeinflussung der aromatischen Östrogenhydroxylierung bei der Ratte. Thesis, University of Tübingen, 1979.
16. Janz D, Schmidt D. Anti-epileptic drugs and failure of oral contraceptives. Lancet 1:1113 (1974).
17. Nenyon IE. Unplanned pregnancy in an epileptic. Br J Med 1:686 (1972).
18. Michot F, Burgi M, Buttner J. Rimactan (rifampicin) und Antikoagulantentherapie. Schweiz Med Wochenshr 100:583 (1970).
19. Self TH, Mann RB. Warfarin and rifampicin interaction. Chest 67:490 (1975).
20. Sivalahari ET, Pihlajamaki KK, llsalo EJ. Rifampicin and drug metabolism. Lancet 2:232 (1974).
21. Zilly W, Breimer DD, Richter R. Induction of drug metabolism in man after rifampicin treatment measured by increased hexobarbital and tolbutamide clearance. Eur J Clin Pharmacol 9:219 (1975).
22. Zilly W, Breimer DD, Richter E. Stimulation of drug metabolism by rifampicin in patients with cirrhosis or cholestasis measured by increased hexobarbital and tolbutamide clearance. Eur J Clin Pharmacol 11:287 (1977).
23. Peters U, Hausamen TU, Grosse-Brockhoff F. Einfluss von Tuberkulostatika auf die Pharmakokinetik des Digitoxins.
44. Feminisation in liver disease. Editorial. Lancet 2:408 (1976).
45. Zumoff B, Fishman J, Gallagher TF, Hellman L. Estradiol metabolism and cirrhosis. J Clin Invest 47:20 (1968).
46. Lopez del Pino V, Bolt HM. Die thioacetamid-vergifte Ratte als tierexperimentelles Modell für endokrinologische Untersuchungen des Oestrogenstoffwechsels unter chronischer Leberschädigung. Endokrinologie 66:250 (1975).
47. Lopez del Pino V, Bolt HM. Der zeitliche Verlauf der durch Thioacetamid induzierten Veränderungen des Oestrogenstoffwechsels in der Rattenleber. Endokrinologie 68:137 (1976).
48. Lopez del Pino V, Bolt HM. Effect of hepatotoxic agents on hepatic microsomal metabolism of estrogens in the rat. Arzneim-Forsch Drug Res 27:2117 (1977).
49. Sandberg AA, Slunwhite WR. Studies on phenolic steroids. II. The metabolic fate and hepatobiliary-enteric circulation of 14C-estrone and 14C-estradiol in women. J Clin Invest 36:1206 (1957).
50. Bolt W, Ritzel F, Bolt HM. Enterohepatischer Kreislauf und Sexualhormon-Stoffwechsel beim Menschen. Münch Med Wochenschr 108:875 (1966).
51. Adlercreutz H, Martin F, Tikkanen MJ, Pulkinnen M. Effect of ampicillin administration on the excretion of 12 oestrogens in pregnancy urine. Acta Endocrinol 80:551 (1975).