J. Lab. Clin. Med.
April, 1980

Impaired elimination of caffeine by oral contraceptive steroids

RASHMI V. PATWARDHAN, PAUL V. DESMOND, RAYMOND F. JOHNSON, and STEVEN SCHENKER *Nashville, Tenn.*

The effect of OCS on the disposition and elimination of caffeine was examined. Caffeine (250 mg) was administered orally to 13 healthy males, nine healthy females taking no OCS, and nine healthy females on OCS. The $t_{1/2(\beta)}$ was significantly prolonged in women on OCS (10.7 ± 3.0 hr vs. 6.2 ± 1.6) ($p < 0.001$) as compared to women taking no OCS. Women on OCS had a significantly lower total plasma clearance (0.79 ± 0.21 ml/min/kg vs. 1.3 ± 0.35) and free clearance (1.12 ± 0.28 ml/min/kg vs. 1.97 ± 0.57) than women not taking OCS. Volumes of distribution and plasma binding were similar in both groups of females. When women taking no OCS were compared with men, all pharmacokinetic parameters were similar except for volume of distribution, which was significantly larger in the women ($p < 0.05$). We conclude that OCS impair the elimination of caffeine. (J LAB CLIN MED 95:603, 1980.)

Abbreviations: oral contraceptive steroids (OCS), elimination half-life ($t_{1/2(\beta)}$), aminopyrine breath test (ABT)

Caffeine is extensively used as a therapeutic agent in many prescription and nonprescription medications and is widely consumed in the form of caffeine-containing beverages, i.e., coffee, tea, and numerous carbonated soft drinks. Caffeine, like other related xanthines, has been shown to affect many organ systems, and it stimulates the central nervous system[1] and cardiovascular system.[2] It also has widespread effects on various metabolic processes by its phosphodiesterase-inhibiting action and subsequent stimulation of the cyclic AMP–mediated systems.[3, 4] Neims et al.[5] and Kling and Christensen[6] have shown that there is a prolongation in elimination of caffeine during pregnancy (especially in the later stages) and that this returns to normal following delivery.[5] It is possible that changes in the hormonal milieu (increased estrogens and progesterone) explain the altered caffeine elimination in pregnancy by decreasing its hepatic metabolism. The evidence for this hypothesis are the observations that in rats androgens enhance drug elimination by stimulating the activity of microsomal mixed-function oxidases,[7] OCS decrease the metabolism of some drugs,[8] and there are sex-related differences in the metabolism of some drugs.[7, 9, 10] We therefore studied in detail the effects of OCS and female sex on the disposition and elimination of caffeine.

From the Department of Medicine, Vanderbilt University School of Medicine and Nashville Veterans Administration Medical Center, Nashville, Tenn.
Supported by the Medical Research Service of the Veterans Administration and NIH Grant AA00267.
Submitted for publication Sept. 24, 1979; accepted Dec. 19, 1979.
Reprint requests: Steven Schenker, M.D., V. A. Medical Center, 1310 24th Avenue South, Nashville, Tenn. 37203.

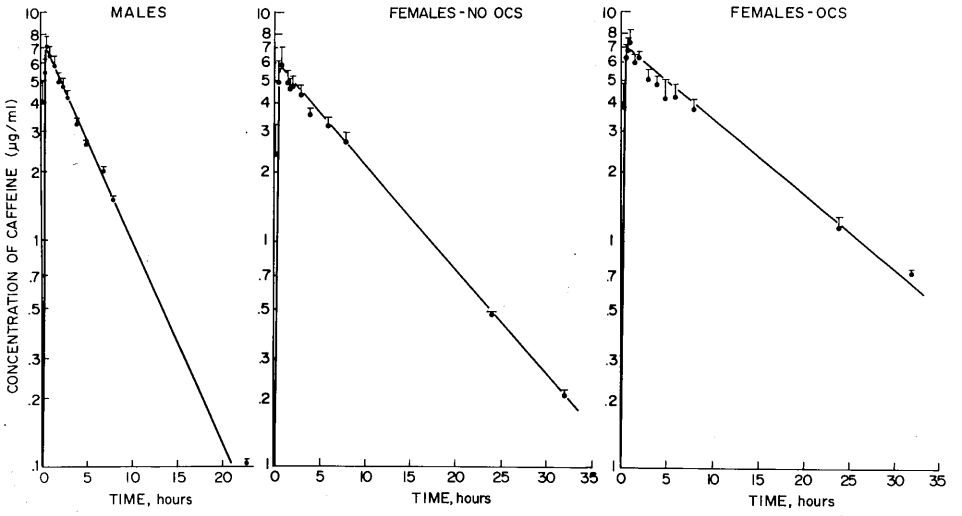

Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean ± S.E.).

Materials and methods

Our subjects were 13 normal males (age range 18 to 71 years; mean weight ± S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight ± S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight ± S.D. 58.4 ± 9.6 kg) who had been on OCS for more than 6 months. Five of the 9 normal women not taking OCS were studied during the second half of their menstrual cycle and 4 during the first half. All subjects studied had a normal clinical history, physical examination, and sequential multiple analyzer of 12 vital determinations (SMA_{12}) profiles and, apart from oral contraceptives as indicated above, had taken no drugs or alcohol for at least 2 weeks prior to the study. Smokers were not included in this study. The OCS included Ovral (norgestrel 0.5 mg, ethinyl estradiol 50 μg; Wyeth Laboratories, Philadelphia, Pa.), Ortho-Novum 1/80-21 (norethindrone 1 mg, mestranol 80 μg; Ortho Pharmaceutical Co., Raritan, N. J.), Modicon #28 (norethindrone 0.5 mg, ethinyl estradiol 35 μg; Ortho), Demulen (ethynodiol diacetate 1 mg, ethinyl estradiol 50 μg; Searle Laboratories, Chicago, Ill.), and Norlestrin (norethindrone acetate 1 mg, ethinyl estradiol 50 μg; Parke, Davis & Co., Detroit, Mich.). All individuals gave written consent for the study, which was approved by the institutional committee for the protection of human subjects. All subjects, who were moderate coffee drinkers (2 to 4 cups/day), had abstained from caffeine-containing beverages and medication for at least 2 days prior to study. (No caffeine was detected in the zero-time blood samples of the subjects studied.) After an overnight fast the subjects received 250 mg of caffeine (approximately equivalent to 3 cups of coffee) in a capsule with 150 ml of water. Blood samples were collected into heparinized glass tubes from an indwelling venous cannula at 15, 30, 45 min and 1, 1½, 2, 3, 4, 5, 6, 7, 8, 24, 32, and 48 hr. The plasma was separated and stored at −20° C until analyzed.

The plasma caffeine concentration was determined by high-performance liquid chromatography (Waters Associates, Inc., Milford, Mass.) as reported by Robertson et al.[2] The $t_{½(\beta)}$ for caffeine was determined by linear regression of the logarithm of the plasma concentration and time of the 1 to 48 hr data. The apparent oral plasma clearance was calculated from the equation[11]: Cl = Dose/AUC_0 where Cl is the apparent oral plasma clearance and AUC_0, as estimated by trapezoidal rule, is the area under the plasma concentration/time curve. Since the drug was administered orally, two estimates were obtained of the apparent volume of distribution (Vd) of caffeine, with realization that these calculations would be biased by the absorption process. The equations used for this purpose were as follows:

$$Vd_{(\beta)} = \frac{\text{Dose } t_{½}}{0.693\ AUC_0}$$

Table I. Pharmacokinetic parameters of caffeine (250 mg) in males, females, and females on OCS

	Normal males (n = 13)	*Normal females taking no OCS* (n = 9)	*Normal females on OCS* (n = 9)
$t½_{(\beta)}$ (hr)	5.5 ± 2.6	6.2 ± 1.6	10.7 ± 3.0†
$Vd_{(\beta)}$ (L/kg)	0.54 ± 0.18	0.69 ± 0.16*	0.72 ± 0.24
$Vd_{(extrap)}$ (L/kg)	0.54 ± 0.13	0.70 ± 0.14*	0.75 ± 0.28
Plasma clearance (ml/min/kg)	1.3 ± 0.42	1.3 ± 0.35	0.79 ± 0.21†
Plasma binding (%)	31.4 ± 1.9	31.5 ± 4.5	29.35 ± 2.17
Plasma clearance of unbound drug (ml/min/kg)	1.8 ± 0.6	1.97 ± 0.57	1.12 ± 0.28†

Values are mean ± S.D.
*$p < 0.05$ for normal males vs females taking no OCS.
†$p < 0.001$ for females taking no OCS vs. females on OCS.

and

$$Vd_{(extrap)} = \frac{Dose}{Cp_{(o)}}$$

where Cp(o) is the plasma caffeine concentration at zero time obtained by back extrapolation of the exponential disappearance curve and AUC_0 is as defined above.

The plasma binding of caffeine was determined by equilibrium dialysis with plasma collected immediately before the study. Equilibrium dialysis was carried out at room temperature against 0.067M phosphate buffer, pH 7.4, in an equilibrium dialyzing Teflon cell system (Spectrum Medical Industries, Inc., New York, N. Y.) with a cellulose membrane. Preliminary experiments have indicated that 3 hr was sufficient time for equilibrium to be achieved, and binding was determined over the concentration range 2.5 to 10.0 μg/ml, with the use of [G-^{3}H]-radiolabeled drug (sp. act. 114 mCi/mg; purity greater than 98%; Amersham Corp., Chicago, Ill.).

The values for the various subject groups were compared by the unpaired two-tailed Student's t test, and $p < 0.05$ was taken as the minimum level of significance.

Results

The rate of caffeine absorption was rapid and equal in all three groups, and peak blood levels were reached within 30 to 60 min, after which time the concentration declined monoexponentially. There were no significant differences in the time to peak and the peak levels of caffeine, and the plasma concentration-time profiles (Fig. 1) were qualitatively similar in all groups. Differences in absorption therefore did not play a role in the altered pharmacokinetics which were observed and are described below.

The pharmacokinetic parameters in the three groups, i.e., males, females and females on OCS are shown in Table I. The $t½_{(\beta)}$ was significantly longer in females on OCS than in females not taking OCS (10.7 ± 3.0 hr vs. 6.2 ± 1.6) ($p < 0.001$). Total plasma clearance (bound and unbound drug) was also significantly less ($p < 0.001$) in women on OCS than in females not taking OCS. Plasma binding of caffeine (31.5% ± 4.5 and 29.35% ± 2.17) and volumes of distribution ($Vd_{(\beta)}$ = 0.69 ± 0.16 ml/min/kg and 0.72 ± 0.24 and $Vd_{(extrap)}$ = 0.70 ± 0.14 and 0.75 ± 0.28) were similar in both groups of females. Free clearance or clearance of unbound drug (clearance of unbound drug = plasma clearance/unbound fraction of drug) was significantly less in females on OCS ($p < 0.001$) when the two groups of females were compared.

In the comparison of males and females taking no OCS, there was no significant difference in the $t½_{(\beta)}$ (5.5 ± 2.6 hr and 6.2 ± 1.6). Although the volumes of distribution,

$Vd_{(\beta)}$ and $Vd_{(extrap)}$, were larger in females not taking OCS compared to the males ($p < 0.05$), there were no differences in total plasma clearance (1.3 ± 0.42 ml/min/kg and 1.3 ± 0.35), plasma binding (31.4% ± 1.9 and 31.5% ± 4.5), and free clearance (1.8 ± 0.6 ml/min/kg and 1.97 ± 0.57).

Comparison of eight normal males 18 to 35 years old vs. seven normal males 35 to 71 years old revealed no significant differences in $t\frac{1}{2}(\beta)$, volume of distribution ($Vd(\beta)$, or total clearance of caffeine. There was a slight (32.43% ± 1.62 to 29.89% ± 1.13) (mean ± S.D.) decrease in plasma caffeine binding in the older group ($p < 0.01$). This suggests that aging does not importantly alter caffeine elimination.

In the small group of females not taking OCS there were no differences in any pharmacokinetic parameters, when women in the first half of the menstrual cycle were compared with women studied in the second half of the menstrual cycle.

The $t\frac{1}{2}(\beta)$ was significantly longer ($p < 0.001$) and the plasma clearance and free clearance were significantly less ($p < 0.001$) in women on OCS than in the males. The volumes of distribution and plasma caffeine binding were similar in males and females on OCS.

Discussion

In our study, OCS markedly altered the pharmacokinetics of caffeine. The $t\frac{1}{2}(\beta)$ was almost twice as long (94% longer) in women on OCS than in women not taking OCS, whereas the total plasma clearance was 40% less in females on OCS. The longer $t\frac{1}{2}(\beta)$ is due to reduction in total plasma clearance in the absence of any changes in the volumes of distribution. Plasma caffeine binding was similar in both groups of females, hence the free clearance (clearance of unbound drug) was also 40% lower in females on OCS. Since free clearance best reflects the metabolizing capacity of the liver for caffeine,[11] this reduced free clearance implies that the metabolism of caffeine would be impaired in women on OCS.[11]

Caffeine is rapidly absorbed after oral administration and is evenly distributed in the body proportionally to the water content of the tissue.[12] In humans less than 2% of the administered dose is excreted unchanged in the urine, and the removal from plasma appears to be dependent on the activity of drug-metabolizing enzymes in the liver, involving the cytochrome P-450 mono-oxygenase system.[13] However, data by Aldridge et al.[13] indicate that caffeine is a better substrate for cytochrome P_1-450 than for the form(s) of cytochrome P-450 induced by phenobarbital. Similar observations were made by Lohmann and Meich[14] in their in vitro investigation of the metabolism of another methylxanthine, theophylline.

There is evidence in animal studies that OCS in vitro competitively inhibit microsomal enzymes,[15] but the concentration resulting in inhibition are higher than those after OCS. Estrogens are metabolized by the mixed-function oxidase system and, when added to in vitro microsomal enzymes, cause competitive inhibition of the metabolism of hexobarbital, ethylmorphine, and other drugs.[16, 17] In one study,[18] stilbestrol administered to normal men impaired metabolism of meperidine. Field et al.[19] examined the effect of norethindrone on the metabolism of aminopyrine. There were no differences in ABT results in women not taking OCS during each of the 3 weeks of the menstrual cycle; however, norethindrone impaired the ABT during all phases of the menstrual cycle. Pregnant women are subjected to an increased load of estrogens and progesterone, and women on OCS have a greater estrogen and progesterone load than males and females not taking OCS. Thus the observed decrease in clearance of caffeine may be related to the increased estrogen and/or

progesterone load in pregnancy and while taking OCS. It is not clear as to the duration of OCS therapy required to affect drug elimination; however, our subjects were on OCS for 6 months or more. It is speculated here that OCS suppress the mixed-function oxidase system involved in the metabolism of caffeine.

Sex differences in drug metabolism have been reported for chlordiazepoxide,[20] diazepam,[21] and other drugs.[22] However in our studies of caffeine elimination all pharmacokinetic parameters were similar when males were compared to females not taking OCS, except for volumes of distribution (Vd_{β} and $Vd_{(extrap)}$) which were significantly larger ($p < 0.05$) in females not taking OCS. A similar trend was noted by us earlier with chlordiazepoxide.[20] This increase in volume of distribution of caffeine was reflected in a slight (nonsignificant) increase in $t_{1/2(\beta)}$ in females not taking OCS. (The lack of difference in caffeine metabolism in females not taking OCS as compared to males may be due to the only modest increase in estrogen and/or progesterone in females not taking OCS as contrasted with women on OCS.)

The clinical significance of these findings relates to the altered pharmacokinetic parameters observed. Thus the prolonged $t_{1/2(\beta)}$ in women on OCS should result in a slower rate of drug elimination and accumulation of caffeine even after modest consumption, i.e., 2 to 4 cups of coffee. Our short-term studies with caffeine also imply that after chronic consumption the reduced plasma clearance in women on OCS should result in a higher steady-state level of caffeine than in females not taking OCS and males. It would also take longer to eliminate the caffeine after stopping the drug. The metabolic effects of caffeine accumulation in women on OCS are presently under investigation in our unit. There have been suggestions of detrimental effects on the outcome of pregnancy in mothers consuming large quantities of caffeine.[23] If all related methylxanthines have similar metabolic pathways, then our observations on caffeine may be pertinent to the therapeutic use of theophylline and other xanthines in patients on OCS.

In summary, this study demonstrates that females on OCS have an impaired elimination capacity for caffeine. With long-term use of caffeine, this should result in the accumulation of caffeine in such individuals, and it would be reasonable therefore to recommend that women on OCS and pregnant mothers should moderate their intake of caffeine.

REFERENCES

1. Ritchie JM: Central nervous system stimulants. *In:* The Pharmacological Basis of Therapeutics, ed. 4, Goodman LS and Gilman A, editors. New York, 1970, The MacMillan Co., pp. 358-370.
2. Robertson D, Frolich JC, Carr RK, Watson JT, Hollifield JW, Shand DG, and Oates JA: Effects of caffeine on plasma renin activity, catecholamines and blood pressure. N Engl J Med **298:**181, 1978.
3. Bellet S, Kershbaum A, and Finde EM: Response of free fatty acids to coffee and caffeine. Metabolism **17:**702, 1968.
4. Oberman Z, Herzberg M, Jaskolka H, Harell A, Hoerer E, and Laurian L: Changes in plasma cortisol, glucose and free fatty acids after caffeine ingestion in obese women. Isr J Med Sci **11:**33, 1975.
5. Neims AH, Bailey J, and Aldridge A: Disposition of caffeine during and after pregnancy. Clin Res **27:**236A, 1979.
6. Kling OR and Christensen HD: Caffeine elimination in late pregnancy. Fed Proc **38:**266, 1979.
7. Kato R: Sex related differences in drug metabolism. Drug Metab Rev **3:**1, 1974.
8. Jori A, Bianchetti A, and Prestini PE: Effect of contraceptive agents on drug metabolism. Eur J Pharmacol **7:**196, 1969.
9. Goble FC: Sex as a factor in metabolism, toxicity, and efficacy of pharmacodynamic and chemotherapeutic agents. Adv Pharmacol Chemother **13:**173, 1975.
10. Greenblat DJ, Shader RI, Franke K, MacLaughin DS, Rancil BJ, and Koch-Weser J: Kinetics of

intravenous chlordiazepoxide: sex differences in drug distribution. Clin Pharmacol Ther **22:**893, 1977.
11. Wilkinson GR and Shand DG: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther **18:**377, 1975.
12. Burg AW: Physiological disposition of caffeine. Drug Metab Rev **4:**199, 1975.
13. Aldridge A, Parsons WD, and Neims AH: Stimulation of caffeine metabolism in the rat by 3-methylcholanthrene. Life Sci **21:**967, 1977.
14. Lohmann SM and Meich RP: Theophylline metabolism by the rat liver microsomal system. J Pharmacol Exp Ther **196:**213, 1976.
15. MacKinnon M, Sutherland E, and Simon FE: Effects of ethinyl estradiol on hepatic microsomal proteins and the turnover of cytochrome P-450. J LAB CLIN MED **90:**1096, 1977.
16. Tephly TR and Mannering GJ: Inhibition of microsomal drug metabolism by steroid hormones. Pharmacologist **6:**186, 1964.
17. Tephly TR and Mannering GJ: Inhibition of drug metabolism. V. Inhibition of drug metabolism by steroids. Mol Pharmacol **4:**10, 1968.
18. Rudofsky S and Crawford JS: Some alterations in the pattern of drug metabolism associated with pregnancy, oral contraceptives and the newly-born. Br J Anaesthesiol **38:**446, 1966.
19. Field B, Cherry L, and Hepner GW: Inhibition of hepatic drug metabolism by norethindrone. Clin Pharmacol Ther **25:**196, 1979.
20. Roberts RK, Desmond PV, Wilkinson GR, and Schenker S: Disposition of chlordiazepoxide: sex differences and effects of oral contraceptives. Clin Pharmacol Ther **25:**826, 1979.
21. MacLeod SM, Giles HG, Bengert B, Liu FF, and Sellers EM: Age and gender-related differences in diazepam pharmacokinetics. J Clin Pharmacol **19:**15, 1979.
22. Kato R, Chiesara E, and Frontino G: Influence of sex difference on the pharmacological action and metabolism of some drugs. Biochem Pharmacol **11:**221, 1962.
23. Weathersbee PS, Olsen LK, and Lodge JR: Caffeine and pregnancy. Postgrad Med **62:**64, 1977.