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Impairment of Caffeine Clearance by Chronic Use of Low-Dose Oestrogen-Containing Oral Contraceptives

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Summary. The effect of chronic (> 3 months) administration of low-dose oestrogen-containing (< 50 μg oestrogen) oral contraceptives (OCS) on the pharmacokinetics of caffeine has been examined in a treated females matched with 9 non-smoking, drug-free, healthy control females of similar age, weight and ethnic origin. Each subject received 162 mg caffeine base orally after an overnight fast. OCS subjects had a prolonged elimination half-life of caffeine, (mean 7.88 h vs 5.37 h in the controls). This was the result of marked impairment of the plasma clearance of caffeine (1.05 vs 1.75 ml/min/kg, respectively) with no change in apparent volume of distribution (0.685 in OCS vs 0.750 l/kg in the control group). The absorption parameters determined were peak plasma caffeine concentration (3.99 vs 4.09 μg/ml) and time to peak concentration after drug administration (1.52 vs 0.79), which was moderately prolonged in OCS users. Thus, caffeine clearance, previously reported to be a specific marker of cytochrome P-448 activity in man, is decreased by chronic OCS use. This suggests that OCS may cause significant impairment of this enzyme activity as assessed in vivo. With chronic caffeine consumption, OCS users are predicted to have an increased steady-state plasma caffeine concentration as compared to non-OCS users.

Key words: caffeine, oral contraceptives; pharmacokinetics, elimination half-life

Chronic oral contraceptive steroid (OCS) use has previously been associated with impaired oxidative drug biotransformation in humans. The substrates evaluated have included antipyrine [1, 33], diazepam [3], chlordiazepoxide [29], nitrazepam [19], caffeine [27], theophylline [30, 34], and prednisolone [12]. In contrast, OCS use has been reported either to increase or not to affect the clearance of drugs which undergo hepatic conjugation; drugs of this type evaluated up to now include acetaminophen, lorazepam, and oxazepam [1, 5, 23, 28].

The study of caffeine clearance in humans may provide a probe for specific evaluation in vivo of the effect of low-dose oestrogen OCS on cytochrome P-448 (P_1-450) activity [36]. The present report continues a series of studies of less specifically oxidized substrates, namely antipyrine and diazepam [2, 3], of conjugated substrates (acetaminophen, lorazepam, and oxazepam [1, 5], and an oxidized substrate which undergoes non-restrictive clearance (imipramine; [6]). In these studies, the attempt has been made to control for other factors that have been associated with changes in human drug biotransformation, including age [17], cigarette smoking [13, 26], diet [21], weight [4], ethnic origin [16, 31], and concurrent use of alcohol or other drugs. This was necessary since the best means of evaluating potential drug-drug interactions, namely using each individual as his or her own control by administration of the test substrate in the otherwise drug-free state followed by administration of the test substrate while the subject is exposed to the potentially interacting substance, is both practically and ethically impossible in a population of OCS users.

The present study was concerned with the effect of OCS use on caffeine pharmacokinetics under carefully specified conditions.

Materials and Methods

The subjects were 18 healthy women, 23 to 30 years old, all non-smokers, and all within 20% of their ideal body weight. None were on diets designed for

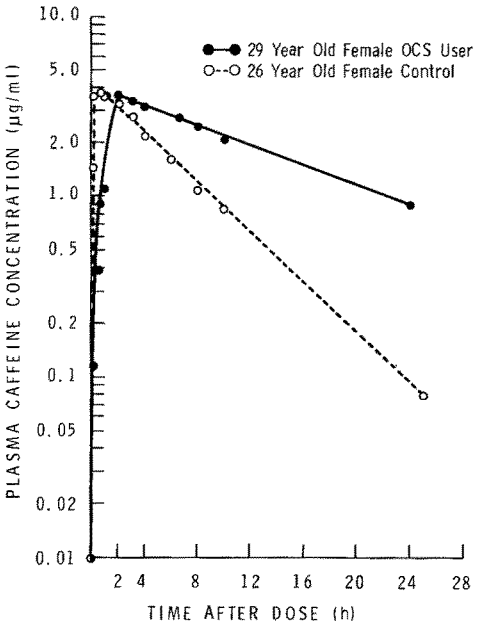

Fig. 1. Plasma caffeine concentrations after oral administration of caffeine to a representative oral contraceptive steroid user and to a matched control subject

Table 1. Subject characteristics and kinetic variables for caffeine in oral contraceptive steroid users and control subjects

	Mean ± SEM	
	OCS Users	Controls
Subject characteristics		
Number	9	9
Age [years]	26 ±1	26 ±1
Weight [kg]	59 ±2	58 ±3
Cigarette Smoking	0	0
Kinetic variables		
Peak Plasma Concentration [μg/ml]	3.99 ± 0.27	4.09 ± 0.24
Time to Peak Concentration [h]	1.52 ± 0.26	0.79 ± 0.11[a]
Elimination half-life [h]	7.88 ± 0.49	5.37 ± 0.62[c]
Apparent Volume of Distribution [l/kg]	0.69 ± 0.03	0.75 ± 0.07
Clearance [ml/min/kg]	1.05 ± 0.10	1.75 ± 0.20[b]

[a] $p < 0.03$;
[b] $p < 0.02$;
[c] $p < 0.005$ by Rank Sum test

weight loss, high protein intake or intensive vitamin supplementation. The subjects were divided into two groups each of 9 for the study. One group consisted of women taking a low-dose oestrogen (50 μg or less of the oestrogen component) oral contraceptive steroid for at least 3 months and no other medication (OCS group). The other group comprised 9 women of similar age not taking any medication. In each group 8 women were Caucasian, and 1 was Black. History, physical and laboratory examination indicated that all subjects were in good health. All subjects were asked to abstain from caffeine consumption 48 hours prior to the study.

After giving written informed consent and fasting overnight, each subject ingested 325 mg citrated caffeine (Lilly) with 100 ml water (equivalent to 162 mg caffeine base). Subjects remained fasting for 3 h after drug administration. Venous blood samples were taken through an indwelling butterfly cannula, kept patent by flushing with a 10 U/ml heparin solution 0.5 ml during the first 10 h after the dose, and by separate venipuncture for the 24 h sample. Samples were collected in heparinized tubes before the dose and after 5, 10, 15, 30, 45 and 60 min, and 2, 3, 4, 6, 8, 10 and 24 h. Plasma was separated and stored at −20 °C until assayed for caffeine concentration.

Caffeine in all plasma samples was determined by high performance liquid chromatography, using UV detection at 280 nm by the method of Blanchard et al. [10]. The internal standard was phenacetin. The analytical instrument was a Waters model 6000 A pump with a reverse-phase C-18 Microbondapack column and a Waters model 440 UV absorbance detector fitted with a 280 nm wavelength filter. The mobile phase was acetonitrile 25%: aqueous buffer (0.01 M acetate pH 4.0) 75% run at a flow rate of 1.8 ml/min. The sensitivity of the method for caffeine was 0.05 μg/ml, and the variation between replicate samples was less than 5%. The retention time for caffeine was 10.25 min, and for phenacetin 7.5 min. No interfering peaks from endogenous plasma constituents or caffeine metabolites were detected.

The pharmacokinetic parameters of caffeine were determined using previously described methods [5, 14, 35]. The exponent from the terminal (beta) phase of the plasma concentration curve was used to calculate the elimination half-life (Fig. 1). The area under the plasma concentration curve from time zero until the final detectable plasma level was determined by the trapezoidal method. To this was added the residual area extrapolated to infinity, calculated as the final concentration divided by the exponent beta, yielding the total area under the plasma concentration curve from time zero to infinity (AUC). Clearance was calculated as dose divided by AUC, assuming complete systemic availability of caffeine after oral administration [11, 24]. The apparent volume of distribution was calculated as clearance divided by beta. Due to the very limited extent of caffeine binding to plasma proteins (35%), non-protein bound parameters were not calculated [9].

Differences between OCS and control subjects were determined by nonparametric analysis using the rank sum test.

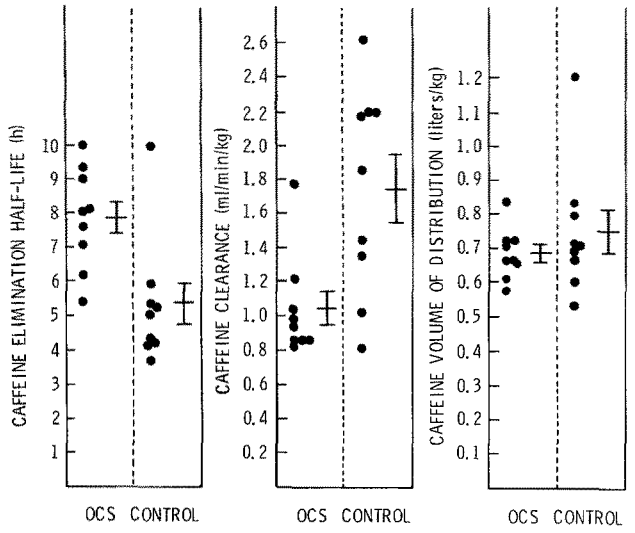

Fig. 2. Caffeine elimination half-life in oral contraceptive steroid users (OCS) and control subjects *(left)*, oral clearance (centre) and oral volume of distribution *(right)*

Results

Plasma caffeine concentrations were well described by rapid absorption followed by monoexponential elimination (Fig. 1). Subject age, weight, smoking status, and ethnic origin were closely matched between the OCS and control groups (Table 1). The elimination half-life of caffeine was markedly prolonged in OCS subjects as compared to controls. This was the result of decreased clearance with no change in total apparent volume of distribution. (Table 1; Fig. 2). The peak plasma concentration after caffeine administration was similar in both groups, although the time to the peak was delayed in OCS users (Table 1).

Discussion

The prolongation in time to peak drug concentration in OCS users suggests a change in gastrointestinal motility and/or absorptive capacity. This has not been observed after oral administration of other drugs, such as acetaminophen and imipramine [1, 6]. Caffeine clearance in humans has been proposed as an in vivo marker of hepatic cytochrome P-448 (P_1-450) activity [36]. Chronic low-dose oestrogen OCS use has previously been demonstrated to impair oxidative biotransformation of other substrates in vivo, including antipyrine [1, 33], diazepam [3], chlordiazepoxide [29], nitrazepam [19], theophylline [30, 34] and prednisolone [12]. These substrates may exhibit different specificity in determination of the profile of in vivo inhibition of drug oxidation by OCS use. Antipyrine clearance in man has been related to overall cytochrome P-450 activity, the formation of specific metabolites being associated with the activity of subspecies of cytochrome P-450 [1, 21, 33]. In any one individual diazepam clearance is highly correlated with antipyrine clearance, suggesting that it, too, is related to overall hepatic cytochrome P-450 activity [17]. Caffeine clearance may provide a more specific probe. In an animal model phenobarbital administration to induce cytochrome P-450 activity resulted in no change in caffeine clearance, while 3-methylcholanthrene, a specific inducer of cytochrome P-448, markedly increased caffeine clearance [7, 8]. In man the same principle may also be true, since potent inducers of cytochrome P-448 (aryl hydrocarbon hydroxylase), such as cigarette smoking, induce the clearance of caffeine to a relatively greater extent than that of antipyrine [26, 36].

A preliminary report by Patwardhan et al. [27] in which the effects on caffeine pharmacokinetics of a variety of OCS preparations of both low and high oestrogen content ($>50\,\mu g$) were studied, is supported by the present investigation in which there was particularly careful subject selection and matching for all variables known to influence oxidative hepatic drug biotransformation [15–17, 21, 26, 31]. In addition, by studying a uniform population of low-dose oestrogen OCS users, it has been demonstrated that the majority of OCS preparations in use in the United States are potent inhibitors of caffeine clearance.

The mechanism of OCS-related inhibition of hepatic drug oxidation is unclear. No good animal model has yet been described for study of progestin and oestrogen effects on drug metabolism at such very low doses. Some oestrogens to bind to hepatic cytochrome P-450 and both oestrogens and progestins can competitively inhibit P-450 activity in vitro. However, the concentrations of oestrogen or progestin required for such an effect is much greater than that found in vivo during OCS treatment [20, 22, 25, 32].

Clinically, these findings mean that the decreased clearance of caffeine in OCS users should result in increased accumulation of caffeine in people who consume a significant amount of caffeine on a frequent basis as, for example, in drinking coffee, tea or caffeinated soft drinks.

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