Eur J Clin Pharmacol (1995) 48 : 161–166

PHARMACOKINETICS AND DISPOSITION

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Influence of ethinylestradiol-containing combination oral contraceptives with gestodene or levonorgestrel on caffeine elimination

Received: 20 September 1994/Accepted in revised form: 16 December 1994

Abstract In a controlled clinical trial, the elimination of caffeine was examined in 20 healthy women prior to and during one cycle of treatment with either of two oral contraceptive formulations, one containing 0.075 mg gestodene and 0.03 mg ethinylestradiol and one containing 0.125 mg levonorgestrel and 0.03 mg ethinylestradiol. In addition, caffeine clearance was determined 1 month after the last intake of the oral contraceptives. Compared with pretreatment values, the clearance of caffeine was reduced by about 54% and 55% after one treatment cycle with gestodene- and the levonorgestrel-containing oral contraceptive, respectively. Other pharmacokinetic parameters of caffeine, such as t_{max} and C_{max}, were not affected. Clearance values returned to pretreatment values 1 month after the last administration of the oral contraceptives. There was no difference in the reduction of caffeine clearance between contraceptive formulations. A small, but significant difference in the AUC(0–24 h) values of ethinylestradiol was noted between both preparations. There was no correlation between the AUC(model) values of caffeine and the AUC(0–24 h) values of ethinylestradiol. In the present study, a somewhat more pronounced effect on the elimination of caffeine was observed than in previous investigations, where several contraceptive steroids were administered only for a period of 2 weeks.

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Key words Caffeine clearance, Oral contraceptives; gestodene, levonorgestrel, ethinylestradiol

Oral contraceptive steroids can influence the metabolism of a number of drugs [1, 2]. Both in animal experiments and in clinical studies, the hepatic clearance of marker drugs, such as theophylline, caffeine, aminopyrine and antipyrine, has been found to be impaired during concomitant treatment with contraceptive steroids, compared with untreated controls [3–6]. Since these marker compounds are almost completely metabolized prior to their elimination from the body, a reduced clearance can be interpreted as an impairment of hepatic cytochrome P-450-dependent enzymes by the contraceptive steroids. In vitro studies with human liver microsomal preparations have shown that contraceptive steroids carrying a 17α-ethinyl side chain can inactivate cytochrome P-450 enzymes. It seems that, after metabolic activation of the ethinyl group, a reactive metabolite is created which may act as a suicide inhibitor [7–10]. However, it is unknown to what extent this inhibition observed in vitro is of relevance for the clinical situation, and whether enzyme inhibition is the predominant underlying mechanism of the reduced clearance of drugs observed during oral contraceptive therapy. It is also conceivable that there is an indirect regulatory action of the steroid hormones on the expression of hepatic P-450 enzymes, probably mediated via growth hormone.

A recently performed in vivo study has revealed an influence of selected contraceptive steroids on caffeine elimination [11]. P-450 IA1/IA2 are the principal isozymes involved in the metabolism of caffeine [12, 13]. It was found that 17α-ethinylestradiol (EE_2) had the strongest effect, while the progestogens levonorgestrel and dienogest had either only little or no effect at all on caffeine clearance. The combination of either of the two progestogens with EE_2, on the other

hand, caused practically the same reduction of caffeine elimination [11, 14].

It was the aim of the present study, to compare the influence of two combination oral contraceptives on the metabolic clearance of caffeine in women. Both oral contraceptive formulations contained the same dose of EE_2 (0.03 mg) and either levonorgestrel or gestodene as progestogenic components. In several in vitro studies gestodene has been described as the progestogen with the highest inhibitory activity [7–10]; it was of interest to examine whether this would apply in vivo.

Subjects and methods

Volunteers

Twenty healthy, young women, (ages 20–34 years), whose weight ranged from 51 to 75 kg, participated in the study. The women had not taken oral contraceptives at least 2 months prior to their participation in the study. The subjects underwent a thorough medical and gynaecological examination before entering the study. Excluded from participation were women who smoked and subjects who had any contraindication for the use of contraceptive steroids. The nature and purpose of the study was explained and written informed consent was given by each participant. The study was approved by the local ethics committees (Ärztekammer Berlin and University of Jena).

Study design

The study was performed as an open group comparison comprising five menstrual cycles: three control cycles (cycles I–III), one treatment cycle (cycle IV) and one post-treatment cycle (cycle V). The subjects were randomly allocated to two groups A and B. Women of group A received the gestodene-containing formulation (0.075 mg gestodene + 0.03 mg EE_2, Femovan, Schering, Berlin) and women of group B the levonorgestrel-containing formulation (0.125 mg levonorgestrel + 0.03 mg EE_2, Minisiston, Jenapharm, Jena) once daily during a treatment cycle of 21 days, respectively. The oral contraceptive was administered in the morning.

In order to assess the intraindividual variation in caffeine elimination, all volunteers received a single oral dose of caffeine on day 21 (±1 day) of each of the three control cycles. On the last day (day 21) of the treatment cycle, as well as on day 21 (± 1 day) of the subsequent post-treatment cycle, the women received another single oral dose of caffeine. The drug (200 mg caffeine as uncoated tablet, Berlin Chemie, Germany) was administered in the morning after an overnight fast, together with 200 ml herbal tea. On day 21 of the treatment cycle, caffeine was administered 30 min after the intake of the oral contraceptive. All volunteers had been instructed to refrain for at least 36 h prior to and during the caffeine test from all methylxanthine-containing beverages and food. Intake of alcohol was also not allowed. Blood samples were collected at the following time points: immediately prior to caffeine intake (0 h) and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 h after administration. All blood samples were allowed to clot at 4°C. The serum was separated by centrifugation and stored at −20°C until analysis.

Analytical determinations

Caffeine

The concentration of caffeine in the serum samples was measured by a specific high-performance liquid chromatography (HPLC) method. To an aliquot of 200 µl of serum, 50 µl of trichloroacetic acid (20%) was added, which contained the internal standard (β-hydroxyethyl-theophylline) at a concentration of 100 µg/ml. After vigorous shaking for 20 s on a vortex mixer and subsequent centrifugation (2500 *g*), 20 µl of the supernatant was injected into the HPLC system. The system consisted of an HPLC pump (Shimadzu, LC-9A), a UV-detector (SPD-6AV), an autosampler (SIL-6B) and an integrator (Chromatopac C-R4AX). A guard column (LiChroCart 4–4, LiChrospher, 60 RP select B, 5 µm) was connected to the analytical column (LiChroCART 125–4, LiChrospher, 100 RP 18, 5 µm). The mobile phase was a mixture of acetonitrile and 0.004 M sodium acetate buffer, pH 4.0 (10:90, v/v). Isocratic elution was performed at a flow rate of 1.0 $m \cdot min^{-1}$ and caffeine was detected by UV absorption at 274 nm. The lower limit of quantification was 0.1 µg/ml with an interassay precision of 4.2% (CV). Precision of the method was evaluated for 1 day as intraday (within day) precision and for a period of days as interday precision. For intra- and interday precision we obtained coefficients of variation of 4.87% and 4.52%, respectively.

Ethinylestradiol

The analysis of EE_2 has been described in detail previously [15]: Analysis was performed in duplicate by a radioimmunoassay using an antiserum raised in rabbits against EE_2-6β-carboxymethyloxime-BSA (Schering) and [6, 7-^{3}H]-EE_2 (specific activity 2.2 TBq/mmol, NEN Products, Boston, Mass., USA) as tracer. Diethylether extracts obtained from 0.3 ml serum were taken for analysis. Assay quality was assessed by the inclusion of quality control samples (50, 125 and 250 $pgml^{-1}$) in each assay. Deviation as measured from nominal values was less than 20%. The lower limit of quantification was 20 $pgml^{-1}$.

Pharmacokinetic evaluation

The serum concentrations of caffeine, which were obtained after single oral administrations on day 21 of the pretreatment, treatment and post-treatment cycles, were evaluated using a one compartment model assuming complete bioavailability (TOPFIT 2.0, Goedecke, Schering, Thomae GmbH, FRG). The elimination half-life ($t_{½}$) of caffeine was determined by regression analysis from the linear terminal part of the semilogarithmic presentation of the caffeine concentration-time curve. The volume of distribution (V_c) was calculated according to:

$$V_c = D / C_0$$

where D is the dose of caffeine administered and C_0 is the serum concentration obtained from extrapolation to time zero. Total clearance (CL) was calculated according to:

$$CL = \ln 2 \times V_c / t_{½}$$

The area under the serum level-time curve of EE_2, AUC(0–24 h), was calculated using the linear trapezoidal rule.

Statistical evaluation

Results are expressed as arithmetic means with (SD). Between-group comparisons of unrelated random samples were performed by means of the Mann-Whitney U-test. Wilcoxon's signed-rank test for paired observations was used to compare the pharmacokinetic parameters of caffeine (CL, $t_{½}$, V_c, C_{max}, t_{max}) obtained from the same subject during the observation period of five cycles. The corresponding parameters of each individual were compared between cycles I and IV, II and IV and III and IV, respectively. The significance level was set to $\alpha = 0.05$ with Bonferroni's correction

for multiple testing. Correlations between AUC(model) values of caffeine and AUC(0–24 h) values of EE_2 were calculated by linear regression and expressed as Spearman's correlation coefficients. Statistical evaluation was by non-parametric tests. The resulting P values indicated that parametric tests would not have yielded other conclusions. All calculations were performed with the statistical software package PC SPSS.

Results

The mean time courses of caffeine levels in the serum of women receiving the gestodene-containing contraceptive formulation are almost identical in cycles I, II, III and V, and there is a clear increase in the corresponding drug levels measured during the treatment cycle IV. The same results were observed in the group of women receiving the levonorgestrel-containing preparation.

Statistical evaluation revealed no significant differences in the pharmacokinetic parameters of caffeine within each of the two treatment groups when pre-treatment cycles I, II and III were compared with the corresponding post-treatment cycle V. However, significant differences ($P < 0.05$) were found in both treatment groups when pre-treatment values of caffeine clearance were compared with the corresponding values obtained during treatment cycle IV (Table 1). V_c was not changed in the group of women who received gestodene-containing pills. Significant differences existed only between cycles I and IV ($P = 0.0125$) and cycles II and IV ($P = 0.0166$) in the group of female volunteers who took levonorgestrel-containing preparations. The other pharmacokinetic parameters of caffeine, C_{max} and t_{max}, were not significantly different within one treatment group prior to, during and after

Table 1 Individual clearance values (ml min^{-1}) of caffeine obtained from 20 women prior to (cycles I–III), during (cycle IV) and after (cycle V) treatment with either the gestodene-containing (group A) or the levonorgestrel-containing oral contraceptive (group B)

Subject	Cycle I	Cycle II	Cycle III	Cycle IV	Cycle V
Group A					
4	39.8	27.9	37.6	28.1	52.2
5	96.4	86.2	114	32.3	79.5
9	150	86.3	125	51.2	131
10	94.6	77.1	73.8	32.2	73.5
11	93.8	104	92.6	43.9	78.5
12	101	94.9	98.8	41.6	89.8
16	76.1	58.1	71.7	33.1	44.4
17	46.1	56.1	37.4	19.7	38.1
19	89.4	87.7	86.6	49.4	107
20	88.8	125	110	50.9	92.6
Means (SD)	87.6 (30.5)	80.3 (27.4)	84.8 (30.1)	38.8* (10.6)	78.7 (28.7)
Group B					
1	110	110	98.7	53.1	109
2	150	137	121	67.9	119
3	79.4	88.0	70.5	33.3	66.0
6	120	58.0	99.4	41.2	93.9
7	104	82.1	115.0	38.3	71.6
8	122	138	138	66.2	24.0
13	81.7	60.3	61.9	32.6	73.0
14	112	180	109	57.6	120
15	84.7	70.7	78.4	40.7	81.6
18	103	74.9	78.1	34.6	65.4
Mean (SD)	107 (21.5)	99.9 (40.3)	97.0 (24.4)	46.6* (13.5)	92.3 (23.8)

*Significantly different ($P < 0.05$) from cycles I, II, III and V

Table 2 Pharmacokinetic parameters of caffeine (means with SD) determined in cycles I–V in women who received either the gestodene-containing formulation (Group A, $n = 10$) or the levonorgestrel-containing formulation (Group B, $n = 10$) during treatment cycle IV, respectively

Parameter	Cycle I	Cycle II	Cycle III	Cycle IV	Cycle V
Group A					
C_{max} (μg/ml)	4.97 (0.88)	5.23 (0.98)	5.15 (0.97)	6.01 (0.39)	5.55 (1.25)
t_{max} (h)	1.96 (0.65)	1.89 (0.98)	1.82 (0.45)	2.60 (1.21)	1.75 (0.80)
$t_{1/2}$ (h)	4.44 (1.48)	4.82 (2.41)	4.66 (2.11)	8.92 (3.08)	4.70 (1.52)
V_c (l)	30.6 (3.72)	29.3 (4.0)	29.8 (3.52)	27.8 (5.2)	28.9 (3.8)
Group B					
C_{max} (μg/ml)	4.28 (0.99)	4.86 (1.18)	4.89 (0.95)	5.10 (0.90)	4.79 (0.87)
t_{max} (h)	2.23 (0.96)	1.66 (0.84)	1.58 (0.77)	1.83 (0.75)	1.79 (0.66)
$t_{1/2}$ (h)	3.32 (0.84)	4.15 (1.59)	3.96 (1.21)	9.15 (2.65)*	4.19 (1.26)
V_c (l)	29.5 (4.5)	31.7 (4.3)	31.2 (3.9)	34.4 (4.73)	31.3 (2.8)

*Significantly different ($P < 0.05$) from cycles I, II, III and V

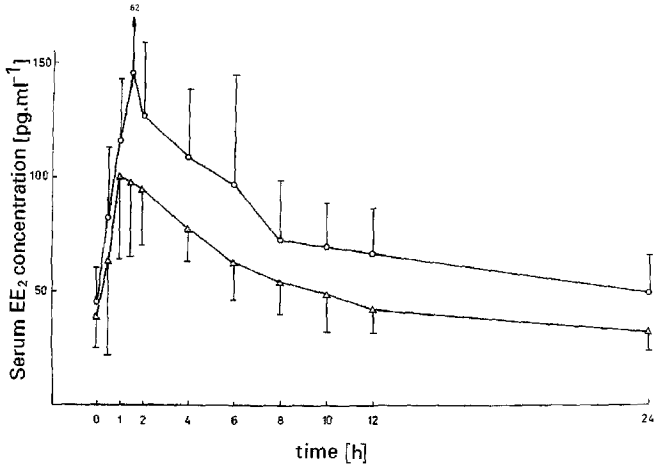

Fig. 1 Mean (SD) concentrations of EE_2 in the serum of women on day 21 of a treatment cycle with the gestodene-containing (*circles*) and the levonorgestrel-containing (*triangles*) oral contraceptive

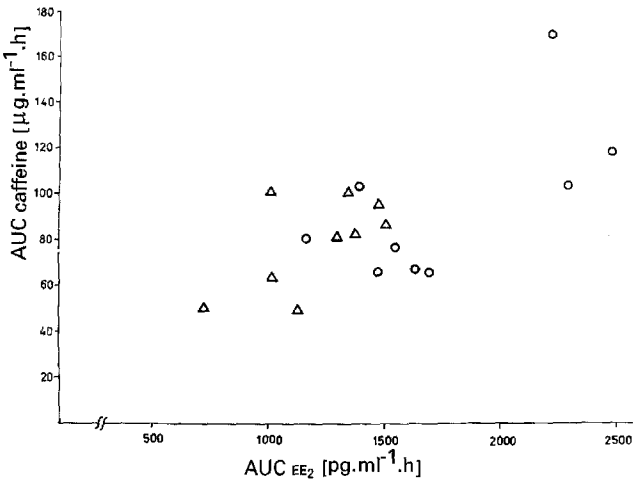

Fig. 2 Correlation coefficient between the AUC(0–24 h) values of ethinylestradiol and the AUC(model) values of caffeine in the group of women receiving gestodene-containing (*circles*) contraceptives ($r = 0.4352$); $P = 0.242$) and levonorgestrel-containing (*triangles*) contraceptives ($r = 0.45$; $P = 0.224$)

intake of the oral contraceptive preparations (Table 2). The extent of reduction in the total clearance of caffeine was found to be about 54% in those women who took the gestodene-containing preparation and about 55% in those women who received the levonorgestrel-containing formulation. There was no difference between these two groups in the extent of clearance reduction.

The mean time courses of EE_2 in the serum of women receiving either of the two oral contraceptives are presented in Fig. 1. The AUC(0–24 h) values were found to be 1773 (458) and 1214 (256) $pg \times ml^{-1} \times h$ in treatment groups A and B, respectively. The corresponding C_{max}values were 148 (59) and 103 (35) $pg\,ml^{-1}$, and were reached 1.8 (0.9) h and 2.2 (1.1) h after drug administration, respectively. There was neither a close correlation between the AUC(model) values of caffeine and the corresponding AUC(0–24 h) values of EE_2 within a treatment group (group A $r = 0.4352$; $P = 0.242$; group B $r = 0.45$, $P = 0.224$), nor were there significant differences in the degree of this correlation between the two groups (Fig. 2). There was, however, a significant difference ($P < 0.05$) in the AUC(0–24 h) values of EE_2 between the two treatment groups.

Discussion

The repeated determination of caffeine elimination in three successive control cycles in healthy women revealed only minor intraindividual variation (CV 28.4%), which was similar to observations made previously in male volunteers [16]. Therefore, a single assessment of caffeine elimination seems to be sufficient to reliably characterize the activity of the responsible cytochrome P-450 enzymes in vivo. Caffeine elimination was markedly reduced after one cycle of treatment with either of the two investigated combination oral contraceptives. However, a treatment-free interval of one cycle was sufficient to restore the caffeine clearance to pretreatment values, irrespective of which of the two oral contraceptives had been taken by the women.

The results of the present study are in good agreement with our own results obtained during a previously performed study on EE_2, levonorgestrel, dienogest and combinations of each of these progestogens with EE_2, and with the results of others, who also found a reduction in the clearance of caffeine during long-term administration of levonorgestrel-containing oral contraceptives [11, 14, 17, 18]. Whereas 2 weeks of daily administration of the progestogen dienogest at a dose of 2 mg, had practically no effect on the caffeine clearance, the administration of levonorgestrel at a daily dose of 0.125 mg over the same time period reduced the caffeine clearance by about 24% as compared with pretreatment values. EE_2, administered at a daily dose of 0.05 mg, caused a reduction in caffeine clearance by about 38%. A combination of 0.05 mg EE_2 with either 2 mg of dienogest or 0.125 mg levonorgestrel, on the other hand, reduced clearance values by about 36% and 34%, respectively [11, 14]. The reduction of caffeine clearance by about 54–55% observed in the present study after 3 weeks of treatment compares well with these results. Obviously, there was no differential effect of levonorgestrel and gestodene on caffeine elimination.

In another study, Rietfeld et al. [4] investigated the influence of different oral contraceptives on caffeine clearance in women and noted that the extent of clearance reduction was independent of the kind of progestogen administered; however, there seemed to be an increasing effect with prolonged oral contraceptive treatment. A similar trend was observed in the present study, where a more marked reduction of caffeine

clearance was observed after 3 weeks of treatment compared with our previous investigations, where the oral contraceptives were only administered for a period of 2 weeks [11, 14].

Another aspect of the present study was to examine whether there was a correlation between caffeine AUC(model) determined in each subject on day 21 of the treatment cycle and the corresponding AUC values of EE_2. If there was an inhibition of P-450-dependent enzymes involved in the metabolism of both caffeine and EE_2, a reduction in the clearance of caffeine could have been accompanied by a similar reduction in the clearance of EE_2. In fact, such an observation had been reported for the disposition of theophylline in women who received oral contraceptives [3]. Subjects with a markedly reduced caffeine AUC(model) would be assumed to have generally higher AUC values of EE_2, than those subjects with smaller changes in caffeine AUC(model). However, this was not the case. There are several possible explanations: It might well be that only selected isozymes were affected by the oral contraceptive treatment, which are mainly involved in the metabolism of caffeine and are not of relevance for the metabolism of EE_2. It is also conceivable, however, that changes in the rate of metabolism of caffeine are mainly caused by an indirect effect of the contraceptive steroids on the regulation of the biosynthesis of cytochrome P-450 enzymes.

The maximum serum concentrations of EE_2 observed in treatment group A corresponded well with the results obtained in previous studies with the same oral contraceptive. Typical values measured on day 21 of a treatment cycle with the gestodene-containing preparation were in the range of 120–160 $pg\,ml^{-1}$. The corresponding AUC(0–24 h) values of EE_2 were within a range of 940 to 1557 $pg \times ml^{-1} \times h$ [21–23]. Thus, the mean AUC value observed in the present study was only slightly above this range. Since the corresponding concentration values of EE_2 during one cycle of treatment with the levonorgestrel-containing preparation were not available, the present results cannot put into perspective.

A significant difference was found when the AUC values of EE_2 were compared between the two treatment groups. It seems unlikely that this difference was due to differences in the interaction of the two progestogens with EE_2, as has been observed in a similar study previously [19]. In fact, it is generally accepted, and has been demonstrated recently for two particular progestogens, that the EE_2 levels in the serum are independent of the kind of progestogen co-administered [20–23].

In conclusion, it has been demonstrated that during treatment with two different combination oral contraceptives the clearance of caffeine was reduced to about 50% of corresponding pretreatment values. The extent of clearance impairment was independent of the kind of progestogen co-administered. The mechanistic basis of the change in caffeine clearance during oral contraceptive therapy is still poorly understood. In particular, it remains unknown whether the inhibition of cytochrome P-450 enzymes by contraceptive steroids observed in vitro is of relevance for the in vivo situation. In the present investigation, at least, differences in the in vitro inhibitory potential of the two progestogens levonorgestrel and gestodene did not find a correlate in vivo.

Acknowledgement We are indebted to Miss U. Müller for her assistance in the statistical evaluation.

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