Eur J Clin Pharmacol (1984) 26: 371–373

European Journal of Clinical Pharmacology
© Springer-Verlag 1984

Rapid Onset of an Increase in Caffeine Residence Time in Young Women due to Oral Contraceptive Steroids

E. C. Rietveld, M. M. M. Broekman, J. J. G. Houben, T. K. A. B. Eskes[1], and J. M. van Rossum

Departments of Pharmacology and Obstetrics/Gynecology[1], Roman Catholic University of Nijmegen, Nijmegen, The Netherlands

Summary. Oral contraceptive steroids increased the residence time of caffeine in 9 young women by a factor of 2. The effect was already manifested during the first cycle 2 weeks after starting oral contraceptive steroids (OCS) and was slightly increased in the second cycle, after 6 weeks on OCS. Toxic effects attributed to oral contraceptive steroids may in part be indirect and due to prolonged retention of absorbed toxic agents to which women are exposed.

Key words: caffeine, contraceptives; residence time, toxic effects

In the course of a study on the bioavailability of different dosage forms of theophylline, in which students were used in a self-matching design, it was noted that the half-life of theophylline in 2 young females was much longer after the second dose. Furthermore, although they denied having drunk caffeine-containing beverages for the 2 days before the study, caffeine was present in their plasma in considerable amounts. The cause of these unexpected findings appeared to be recent use of a contraceptive steroid combination.

It is known that long-term use of oral contraceptive steroids (OCS) may diminish the elimination kinetics of several drugs; OCS use by women increased the serum half-life of phenazone [1, 2, 3, 4], aminophenazone [5, 6] and methaqualone [7]. Diazepam clearance is also reduced by OCS [8], as is that of chlordiazepoxide [9]. The elimination of caffeine is impaired by OCS [10], but it is not known how rapidly this interference can develop.

The influence of the contraceptive pill has been studied in young women who had not previously used oral contraceptive steroids or who had not taken the pill for at least 3 months. The kinetics of caffeine before and during pill use was studied in the same individuals using a control systems dynamics approach [11].

Materials and Methods

Nine healthy young women participated in the study. Their clinical details are given in Table 1. All were regular drinkers of coffee. Five had never used a contraceptive steroid and four had stopped taking the pill for 3 months to 3 years. Each participant signed written consent to the experiment and was paid.

The participants took 250 mg Caffeine monohydrate (229 mg caffeine) in 100 ml water before (Phase 1) and 2 weeks (Phase 2) and 6 weeks (Phase 3) after taking a contraceptive steroid. The choice of OCS was left to the physician or gynecologist: see Table 1. Blood samples 10 ml were taken using Monovette syringes and Monoject needles just before and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 14 and 24 h after the ingestion of caffeine. Caffeine was determined by GLC, using a glass column packed with 5% OV-17 on 80–100 mesh Gaschrom Q in a HP 5710 gaschromatograph equipped with a N-FID detector [12].

The plasma curves of caffeine were fitted to the sum of exponentials, $C(t) = A_i \cdot e^{-t/\tau_i}$. From the calculated AUC ($\Sigma A_i \tau_i$) and TAUC ($\Sigma A_i \tau_i^2$) the mean residence time (MRT = TAUC/AUC) was calculated. The overall MRT is the sum of the mean residence time of caffeine in the body and the mean time of absorption [11].

Table 1. Details of subjects at the start of the study

Subject	Age [years]	Weight [kg]	Smoker	Previous OCS user	Choice of OCS	Progestagen/ethynyloestradiol [mg]
T.K.	35	62	no	yes (2 y)	Lyndiol (21)	lynestrenol 2.5/0.05
M.F.	28	51	yes	yes (3 m)	Lyndiol (21)	lynestrenol 2.5/0.05
I.K.	22	53	no	yes (2 y)	Stediril (21)	norgestrel 0.5/0.05
M.C.	21	55	no	no	Ovulen 50 (21)	ethynodioldiac 1/0.05
M.B.	20	75	no	no	Ovulen 50 (21)	ethynodioldiac 1/0.05
B.E.	24	45	no	yes (3 y)	Microgynon '50' (21)	levonorgestrel 0.125/0.05
E.K.	20	52	no	no	Microgynon '30' (21)	levonorgestrel 0.15/0.03
N.C.	18	51	no	no	Microgynon '30' (21)	levonorgestrel 0.15/0.03
L.F.	18	69	yes	no	Stediril 150/30 (21)	levonorgestrel 0.15/0.03

Table 2. Influence of oral contraceptive steroids (OCS) on mean residence time and AUC of caffeine in young women

Subject	Time of cycle [weeks]	Before OCS use		After 2 weeks on OCS			After 6 weeks on OCS		
		AUC [mg.h/l]	MRT [h]	AUC [mg.h/l]	MRT [h]	Weight change [kg]	AUC [mg.h/l]	MRT [h]	Weight change [kg]
T.K.	2	49.8	6.7	65.2	9.6	0	98.7	14.1	5
M.F.	3	38.9	5.0	67.1	8.7	0	69.1	10.3	2
I.K.	2	53.9	6.9	247.8[a]	16.9[a]	1	121.7	14.2	−0.5
M.C.	3	30.9	4.8	74.3	10.0	0	91.9	11.7	1
M.B.	4	30.4	5.7	50.3	7.8	0	52.0	8.4	2
B.E.	3	40.1	4.7	82.5	8.5	0	100.6	11.3	1
E.K.	3	34.1	4.7	65.3	9.5	0	69.5	9.3	1
N.C.	1	57.2	7.4	107.1	12.3	0	96.5	12.2	−0.5
L.F.	4	30.4	6.3	50.3	7.2	10	52.0	8.5	10
Mean		40.6	5.8	70.3	9.2	1.2	83.6	11.1	2.3

[a] Data not used in calculation of mean, because subject accidently drunk a caffeine-containing beverage

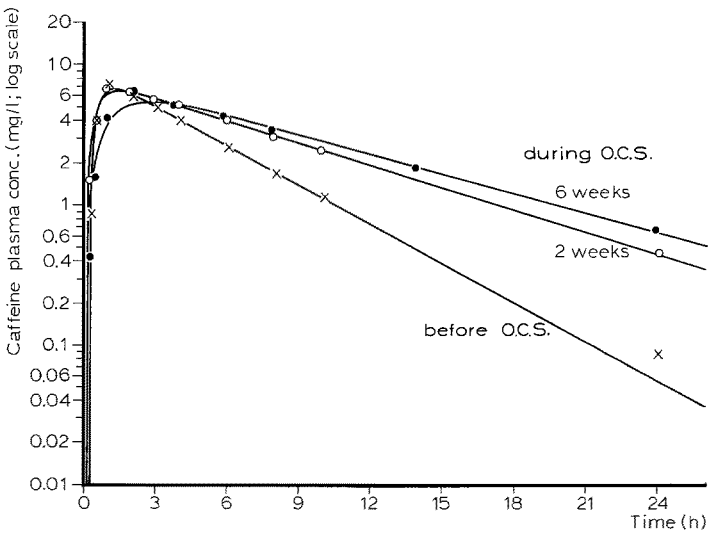

Fig. 1. Plasma levels of caffeine after an oral dose of 229 mg in female subject MF 2 days before and 2 and 6 weeks after starting to take an oral contraceptive steroid. The curves were fitted to the sum of 2 or 3 exponentials using the nonlinear computer program Farmfit. The area under the curve and the overall mean residence time were calculated from the fitted curves. The results are given in Table 2

Results

The plasma profiles of caffeine in the 3 phases of the study in one of the subjects are given in Fig. 1. Similar curves were obtained with all 9 females. The overall kinetic systems parameters, the area under the curve (AUC) and the overall mean residence time (MRT), as calculated from these curves, are given in Table 2.

In all women the MRT was already substantially increased after 2 weeks on OCS. After 6 weeks in most cases there was a further increase. The AUC, too, was increased both after 2 and 6 weeks (Table 2). If the absorption of caffeine from the GI tract were

complete, the mean clearance would have decrease from 5.6 l/h before the oral contraceptive steroids to 3.26 l/h after 2 weeks, and to 2.74 l/h after 6 weeks. If the mean absorption time would unchanged during the course of the 6 weeks, the total volume of distribution would not be significantly changed. The onset of the effect of OCS on the kinetics of caffeine was very rapid.

Discussion

The present study has not only confirmed previous investigations of the effect of OCS studies on the elimination kinetics of phenazone [1–4] and caffeine [10], but it has also shown that their action is already clearly apparent within 2 weeks of starting to take the oral contraceptive steroids. The mean residence time of caffeine was practically doubled after 2 weeks, and it showed a further slight increase during the following weeks.

A change in mean residence time reflects a change in the overall body transport function of residence times, and depends on the mean body transit time as well as on the extraction ratio [11]. If absorption is complete it may be concluded that the clearance is correspondingly decreased. This may imply that the extraction decreases when the cardiac output remains constant, or that both change. Further studies are necessary to clarify this point. It is not certain whether the oestrogen or the progestagen in the OCS is responsible for the increased residence time of caffeine. The progestagen norethindrone alone can cause a decrease in aminophenazone clearance [6], but norethindrone also has some oestrogenic activity [13].

It may be concluded that the increased residence time of caffeine caused by oral contraceptive steroids may contribute to the reported toxicity of the latter. Other toxic substances from the environment (e.g. smoke, environmental chemicals, and etc.) may remain in the body much longer in females taking OCS, and so a given exposure will lead to a higher concentration in such women.

In this way some of the toxic effects attributed to the pill may be indirect and so could be avoided by limiting exposure to potentially toxic agents.

Acknowledgement. The work was supported in part by a grant from the Netherlands Asthma Foundation (NAF).

References

1. O'Malley K, Stevenson IH, Crooks J (1972) Impairment of human drug metabolism by oral contraceptive steroids. Clin Pharmacol Ther 13: 552–557
2. Homeida M, Halliwell M, Branch RA (1978) Effects of an oral contraceptive on hepatic size and antipyrine metabolism in premenopausal women. Clin Pharmacol Ther 24: 228–232
3. Abernethy DR, Greenblatt DJ (1981) Impairment of antipyrine metabolism by low-dose oral contraceptive steroids. Clin Pharmacol Ther 29: 106–110
4. Teunissen MWE, Srivastava AK, Breimer DD (1982) Influences of sex and oral contraceptive steroids on antipyrine metabolite formation. Clin Pharmacol Ther 32: 240–246
5. Herz R, Koeltz H, Haemmerli UP, Benes I, Blum A (1978) Inhibition of hepatic demethylation of aminopyrine by oral contraceptive steroids in human. Eur J Clin Invest 8: 27–30
6. Field BE, Lu C, Hepner GW (1979) Inhibition of hepatic drug metabolism by norethindrone. Clin Pharmacol Ther 25: 196–198
7. Oram M, Wilson K, Burnett D (1982) The influence of oral contraceptives on the metabolism of methaqualone in man. Br J Clin Pharmacol 14: 341–345
8. Abernethy DR, Greenblatt DJ, Divoll M, Arendt R, Ochs HR, Shader RI (1982) Impairment of diazepam metabolism by low-dose estrogen-containing oral contraceptive steroids. N Engl J Med 306: 791–792
9. Roberts RR, Desmond PV, Wilkinson GR, Schenker S (1979) Disposition of chlordiazepoxide: sex differences and effects of oral contraceptives. Clin Pharmacol Ther 25: 826–831
10. Patwardhan RV, Desmond PV, Johnson RF, Schenker S (1980) Impaired elimination of caffeine by oral contraceptive steroids. J Lab Clin Med 95: 604–608
11. Van Rossum JM, Burgers J, Van Lingen G, de Bie J (1983) Pharmacokinetics: a dynamic systems approach. Trends Pharmacol Sci 4: 27–30
12. Bonati M, Castelli D, Latini R, Garattini S (1979) Comparison of gas-liquid chromatography with nitrogen-phosphorus selective detection and high-performance liquid chromatography methods for caffeine determination in plasma and tissue. J Chromatogr 164: 109–113
13. Van Kordelaar JMG, Vermorken AMJ, De Weerd CJM, Rossum van JM (1975) Interaction of contraceptive progestins and related compounds with the oestrogen receptor II: effects on ^{3}H-oestradiol binding to the rat uterine receptor in vitro. Acta Endocrinol 78: 165–179

Received: August 5, 1983
accepted: January 6, 1984

Prof. Dr. J. M. van Rossum
Katholieke Universiteit Nijmegen
Faculteit der Geneeskunde en Tandheelkunde
Afdeling Farmacologie
Geert Grooteplein Noord 21
Postbus 9101
NL-6500 HB Nijmegen, The Netherlands