# PHARMACOKINETICS AND DRUG DISPOSITION

# Oral contraceptives containing ethinyl estradiol and gestodene markedly increase plasma concentrations and effects of tizanidine by inhibiting cytochrome P450 1A2

*Background and Objective:* Oral contraceptives (OCs) can inhibit drug metabolism, but their effect on various cytochrome P450 (CYP) enzymes and drugs can be different. Our objective was to study the effect of combined OCs, containing ethinyl estradiol (INN, ethinylestradiol) and gestodene, on CYP1A2 activity, as well as their interaction potential with tizanidine.

*Methods:* In a parallel-group study, 15 healthy women using OCs and 15 healthy women without OCs (control subjects) ingested a single dose of 4 mg tizanidine. Plasma and urine concentrations of tizanidine, as well as several of its metabolites (M-3, M-4, M-5, M-9, and M-10), and pharmacodynamic variables were measured until 24 hours after dosing. As a marker of CYP1A2 activity, an oral caffeine test was performed in both groups.

*Results:* The mean area under the plasma concentration–time curve from time 0 to infinity [AUC(0-∞)] of tizanidine was 3.9 times greater ($P < .001$) and the mean peak plasma tizanidine concentration ($C_{max}$) was 3.0 times higher ($P < .001$) in the OC users than in the control subjects. In 1 OC user the AUC(0-∞) of tizanidine exceeded the mean AUC(0-∞) of the control subjects by nearly 20 times. There were no significant differences in the elimination half-life or time to peak concentration in plasma of tizanidine between the groups. Tizanidine/metabolite ratios in plasma (M-3 and M-4) and urine (M-3, M-4, M-5, M-9, and M-10) were 2 to 10 times higher in the users of OCs than in the control subjects. In the OC group the excretion of unchanged tizanidine into urine was, on average, 3.8 times greater ($P = .008$) than in the control subjects. The plasma caffeine/paraxanthine ratio was 2.8 times higher ($P < .001$) in the OC users than in the control subjects. The caffeine/paraxanthine ratio correlated significantly with the AUC(0-∞) and peak concentration of tizanidine in plasma, with its excretion into urine, and with, for example, the tizanidine/M-3 and tizanidine/M-4 area under the plasma concentration–time curve ratios. Both the systolic and diastolic blood pressures were lowered by tizanidine more in the OC users (−29 ± 10 mm Hg and −21 ± 8 mm Hg, respectively) than in the control subjects (−17 ± 9 mm Hg and −13 ± 5 mm Hg, respectively) ($P < .01$).

*Conclusions:* OCs containing ethinyl estradiol and gestodene increase, to a clinically significant extent, the plasma concentrations and effects of tizanidine, probably mainly by inhibiting its CYP1A2-mediated presystemic metabolism. Care should be exercised when tizanidine is prescribed to OC users. (Clin Pharmacol Ther 2005;78:400-11.)

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Ethinyl estradiol (INN, ethinylestradiol) and gestodene are exogenous female sex steroids commonly used in combined oral contraceptives (OCs). In vitro studies have shown that ethinyl estradiol and some progesto-

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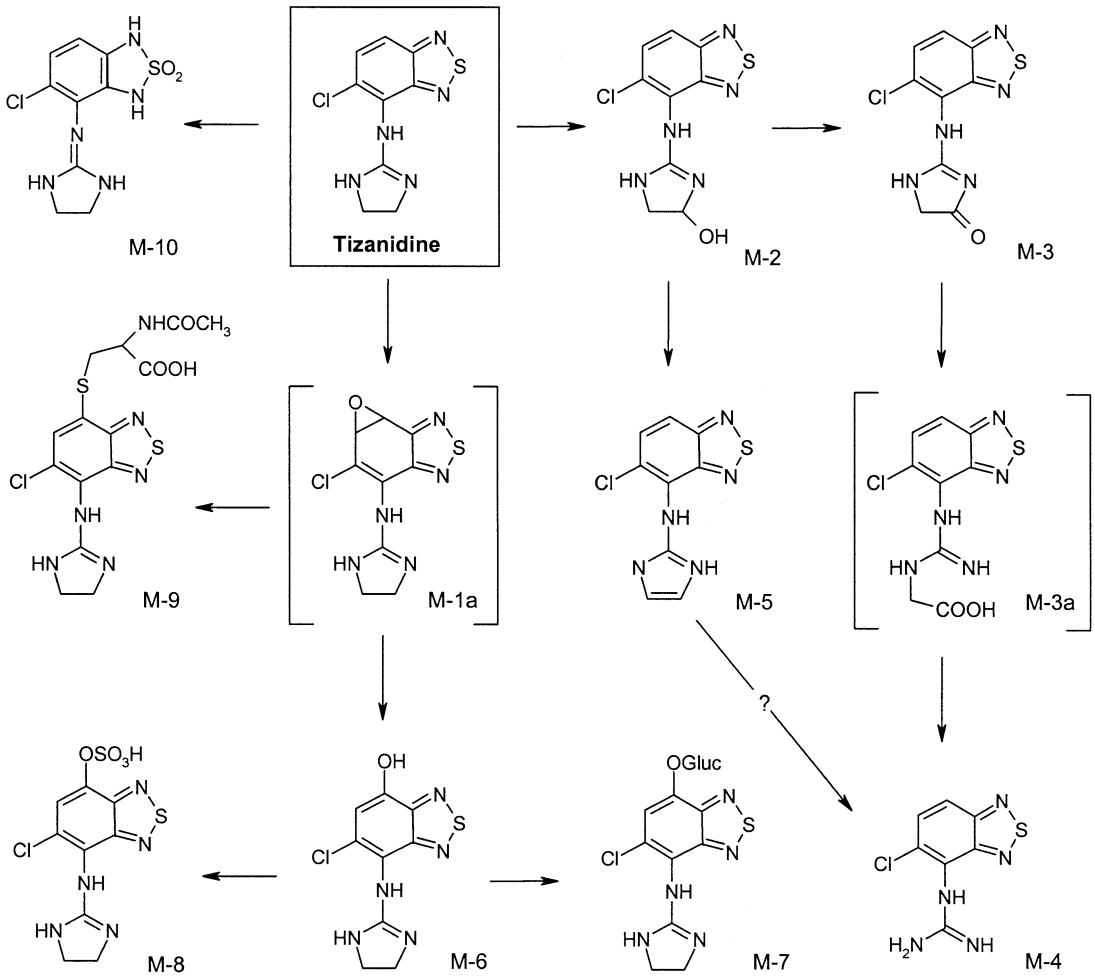


**Fig 1.** Structures of tizanidine and its metabolites and proposed metabolic pathways involved.[24] Figures in *brackets* indicate theoretically possible intermediates.

gens, such as gestodene and desogestrel, can be potent inhibitors of some cytochrome P450 (CYP) enzymes.[1-4] Ethinyl estradiol has a strong inhibitory effect on CYP3A4,[3] CYP2B6,[5] CYP2C9,[6] and CYP2C19[6] in vitro. Gestodene is a potent inhibitor of CYP3A4[2,6] and CYP2C19[4,6] but seems to have no significant effect on CYP1A2 in vitro.[2] In humans concomitant use of OCs has been found to inhibit the metabolism of several, but not all, substrates of CYP1A2,[7-13] CYP3A4,[14-18] and CYP2C19.[19,20]

Tizanidine, an $\alpha_2$-adrenergic agonist, is used as a centrally acting skeletal muscle relaxant. In addition to its use in patients with chronic spasticity conditions, such as multiple sclerosis, tizanidine is commonly used, for example, in patients with tension-type headache and musculoskeletal pain.[21] These conditions are not uncommon in fertile-age women who are likely to use OCs. Tizanidine is eliminated principally by metabolism and has an extensive first-pass metabolism, mediated by CYP1A2.[22,23] Its main metabolites in plasma and urine are M-3 and M-4, which lack pharmacologic activity (Fig 1).[24] Recently, the CYP1A2 inhibitors fluvoxamine and ciprofloxacin were found to strongly increase the plasma concentrations and effects of tizanidine in vivo.[22,23] The caffeine/paraxanthine ratio is a validated index for systemic CYP1A2 activity,[25-27] and OCs have been found to reduce the metabolism of caffeine in humans.[9-12] Tizanidine differs pharmacokinetically from caffeine, for example, by its extensive presystemic metabolism and shorter elimination half-life.[22,25]

The product information for tizanidine states that OCs decrease the clearance of tizanidine by 50%, but this information is based on unpublished data.[28] We

aimed to investigate whether OCs containing ethinyl estradiol and gestodene affect tizanidine pharmacokinetics and whether these effects parallel changes in the caffeine/paraxanthine ratio. Furthermore, by recording the pharmacodynamic effects of tizanidine, we wanted to characterize the clinical significance of the possible interaction. To this end, an OC-tizanidine interaction study, including a caffeine test, was conducted in healthy female volunteers who were either users or nonusers of OCs.

## METHODS

***Subjects and study design.*** The study protocol was approved by the Ethics Committee for Studies in Healthy Subjects of the Hospital District of Helsinki and Uusimaa, Finland, and the Finnish National Agency for Medicines, Helsinki, Finland. This was an open, parallel-group study with 15 healthy female volunteers (mean age, 22 ± 2 years [range, 18-25 years]; mean weight, 57 ± 6 kg [range, 48-63 kg]) using OCs and 15 healthy female volunteers (mean age, 22 ± 2 years [range, 19-26 years]; mean weight, 62 ± 10 kg [range, 52-74 kg]) without any concomitant medication. There were no statistically significant differences in age or weight between the groups.

The combined OCs used by the women in this study contained 75 μg gestodene and either 20 μg ethinyl estradiol (Harmonet tablet [Wyeth, Newbridge, Ireland], 7 subjects; Meliane tablet [Schering, Berlin, Germany], 5 subjects) or 30 μg ethinyl estradiol (Femoden tablet [Schering], 2 subjects; Minulet tablet [Wyeth], 1 subject). The OC users had been using these OC preparations for at least 1 menstrual cycle before the study. Before entering the study, all subjects provided written informed consent and were ascertained to be healthy by medical history, physical examination, and routine laboratory tests. For safety reasons, subjects with a systolic blood pressure lower than 110 mm Hg were excluded from the study. None of the subjects were tobacco smokers, and none used any continuous medication except OCs.

In this study each volunteer received a single dose of tizanidine. On the day of tizanidine administration, the OC users had been taking the OC preparation for 6 to 21 days during that cycle and the control subjects were in a corresponding phase of the menstrual cycle. The users of OCs were instructed to ingest the OC preparation at 8 AM for 6 days before and on the day of tizanidine administration. On the study day, after an overnight fast, a single oral dose of 4 mg tizanidine (one 4-mg Sirdalud tablet; Novartis Pharma, Wehr, Germany) was ingested with 150 mL water at 9 AM. A standard meal was served at 3 and 7 hours after tizanidine ingestion. Drinking of grapefruit juice and tobacco smoking were not allowed for 1 week before the study day. Alcohol and drinks containing caffeine were not permitted on the study day. The subjects were under direct, close medical supervision during the day of administration of tizanidine. Fluids for intravenous infusion were available for immediate use, but they were not needed.

An oral caffeine test[26,27] was performed on the day before the tizanidine study day. The subjects ingested 100 mg caffeine (one 100-mg Cofi-Tabs tablet; Vitabalans, Hämeenlinna, Finland) at 9 AM, after having abstained from caffeine intake for at least 12 hours, and a blood sample for analysis of plasma caffeine and paraxanthine (1,7-dimethylxanthine) concentrations was taken 6 hours after caffeine intake.

***Sampling.*** On the days of administration of tizanidine, a forearm vein of each subject was cannulated with a plastic cannula and kept patent with an obturator. Timed blood samples were drawn before the administration of tizanidine and at 20, 40, 60, and 90 minutes and 2, 3, 4, 5, 7, 9, 12, and 24 hours later. Blood samples (10 mL each) were taken into ethylenediaminetetraacetic acid–containing tubes. Plasma was separated within 30 minutes. The urine was collected cumulatively in 2 fractions: 0 to 12 hours and 12 to 24 hours. Plasma and urine aliquots were stored at −70°C until analysis.

***Drug concentrations in plasma and urine.*** Plasma and urine tizanidine and metabolite concentrations were quantified by use of an API 2000 liquid chromatography–tandem mass spectrometry system (MDS Sciex, Ontario, Canada). Chromatography was performed on an XTerra RP $C_{18}$ column (3.9 × 100 mm; Waters, Milford, Mass) by use of gradient elution. The mobile phase consisted of 10-mmol/L ammonium acetate (pH 9.5, adjusted with 25% ammonia solution) and acetonitrile. The mass spectrometer was operated in the atmospheric pressure chemical ionization mode with positive ion detection. The ion transitions monitored were mass-to-charge ratio (*m/z*) 254 to *m/z* 44 for tizanidine, *m/z* 268 to *m/z* 211 for M-3, *m/z* 228 to *m/z* 211 for M-4, *m/z* 252 to *m/z* 216 for M-5, *m/z* 415 to *m/z* 286 for M-9, *m/z* 288 to *m/z* 188 for M-10, and *m/z* 230 to *m/z* 44 for the internal standard, clonidine. These transitions represent the product ion of the $[M+H]^+$ ion. The limit of quantification for tizanidine was 0.05 ng/mL, and the day-to-day coefficient of variation was 17.4% at 0.1 ng/mL, 6.4% at 1 ng/mL, and 7.5% at 10 ng/mL (n = 8). A signal-to-noise ratio of 10:1 was used as the limit of detection for tizanidine metabolites, and

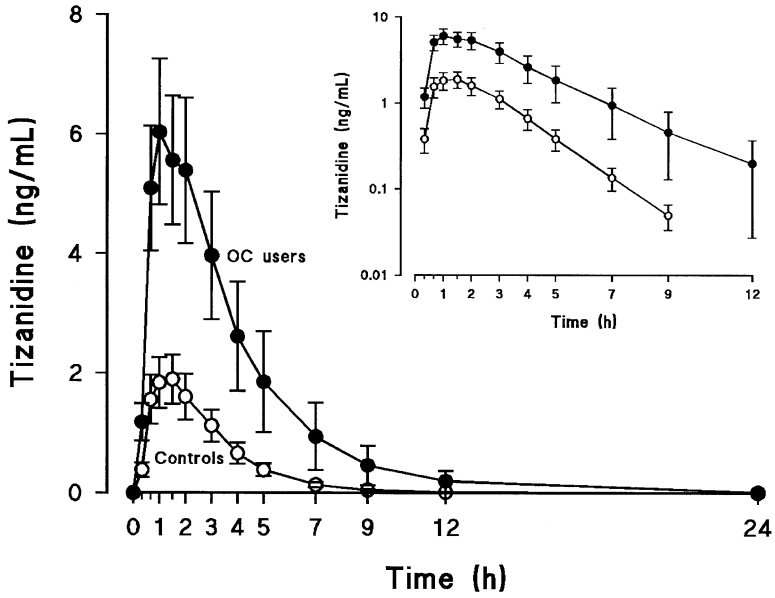


**Fig 2.** Mean (±SEM) plasma concentrations of tizanidine in 15 users of oral contraceptives (OCs) (*solid circles*) and 15 female control subjects (*open circles*) after 4 mg tizanidine. *Inset* depicts same data on a semilogarithmic scale.

the quantities are given in arbitrary units relative to the ratio of the peak height of the metabolite to the peak height of the internal standard. Ethinyl estradiol and gestodene did not interfere with the assay.

Plasma caffeine and paraxanthine concentrations were determined by HPLC, with β-hydroxyethyltheophylline as the internal standard.[29,30] The day-to-day coefficient of variation of caffeine and paraxanthine was less than 6% at relevant concentrations.

***Pharmacokinetics.*** The pharmacokinetics of tizanidine and its metabolites M-3 and M-4 were characterized by peak concentration in plasma ($C_{max}$), time to $C_{max}$ ($t_{max}$), area under the plasma concentration–time curve (AUC) from time 0 to infinity [AUC(0-∞)], and elimination half-life ($t_{½}$) by use of noncompartmental methods as described earlier.[22,23] The amount of tizanidine and its metabolites excreted into the urine within 24 hours (Ae) was calculated. The renal clearance ($CL_{renal}$) of tizanidine was calculated as $CL_{renal}$ = Ae/AUC from 0 to 24 hours.

***Pharmacodynamics.*** Systolic and diastolic blood pressures, heart rate, and 3 psychomotor tests were assessed before administration of tizanidine and immediately after each blood sampling, as described earlier.[22,23] In short, in the Digit Symbol Substitution Test, the number of digits correctly substituted in 2 minutes was recorded. Subjective drowsiness and subjective drug effect were measured with a 100-mm-long horizontal visual analog scale. For each pharmacodynamic variable, the incremental or decremental area under the effect versus time curve from 0 to 12 hours was calculated by use of the linear trapezoidal rule. In addition, the maximum responses in each pharmacodynamic variable were calculated.

***Statistical analysis.*** Results are expressed as mean values ± SD in the tables and text and, for clarity, as mean values ± SEM in the figures. The pharmacokinetic and pharmacodynamic variables between the groups were compared by the *t* test or, in the case of $t_{max}$, with Kruskal-Wallis 1-way ANOVA. Logarithmic transformation of pharmacokinetic variables was done before statistical analysis. For all variables except $t_{max}$, 95% confidence intervals were calculated on the mean differences between groups. The Pearson correlation coefficient was used to investigate possible relationships between tizanidine pharmacokinetic variables, the caffeine/paraxanthine ratio, and changes in pharmacodynamic variables. All of the data were analyzed with the statistical program Systat for Windows, version 6.0.1 (SPSS, Chicago, Ill). The differences were considered statistically significant at $P < .05$.

## RESULTS

***Plasma tizanidine.*** Plasma concentrations of tizanidine were considerably higher in the OC users than in the control subjects (Fig 2). The $C_{max}$ of tizanidine was

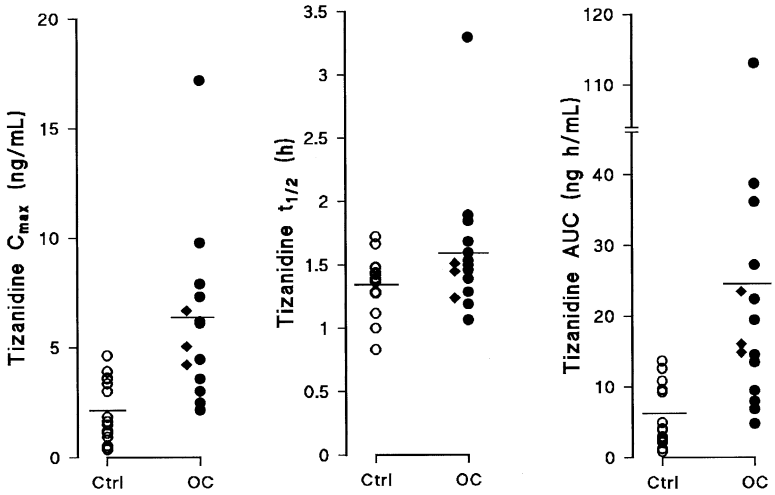


**Fig 3.** Individual and mean values for peak concentration in plasma ($C_{max}$), elimination half-life ($t_{½}$), and area under plasma concentration–time curve from time 0 to infinity (AUC) of tizanidine in 15 users of OCs (*solid circles*, 75 μg gestodene and 20 μg ethinyl estradiol; *diamonds*, 75 μg gestodene and 30 μg ethinyl estradiol) and 15 female control subjects (Ctrl) (*open circles*) after 4 mg tizanidine.

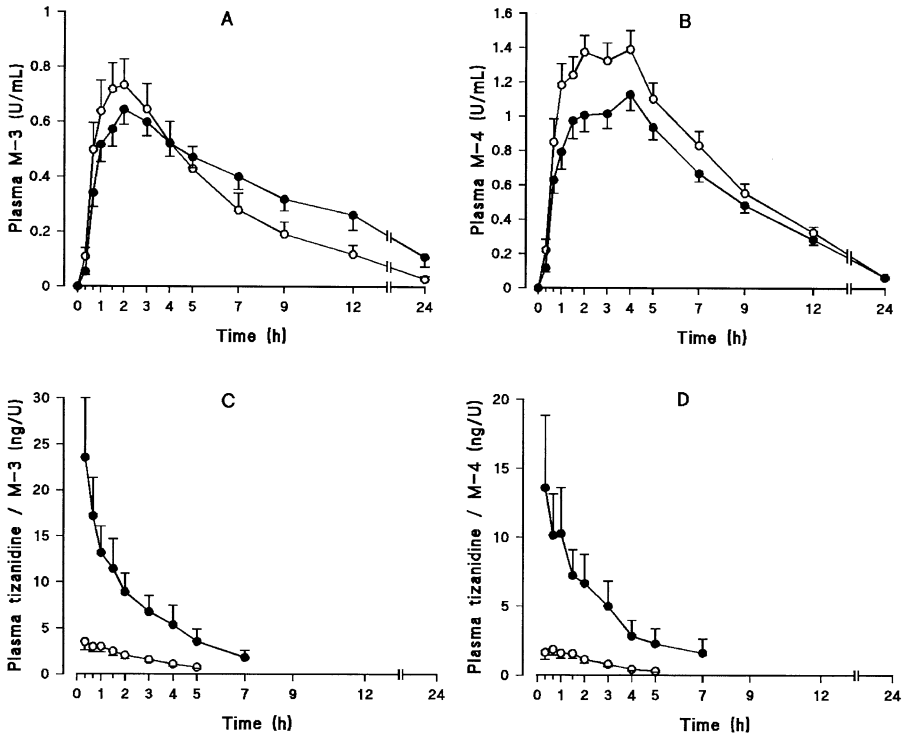


**Fig 4.** Plasma concentrations (mean ± SEM) of tizanidine metabolites M-3 (**A**) and M-4 (**B**), tizanidine/M-3 ratio (**C**), and tizanidine/M-4 ratio (**D**) in 15 users of OCs (*solid circles*) and 15 female control subjects (*open circles*) after 4 mg tizanidine.

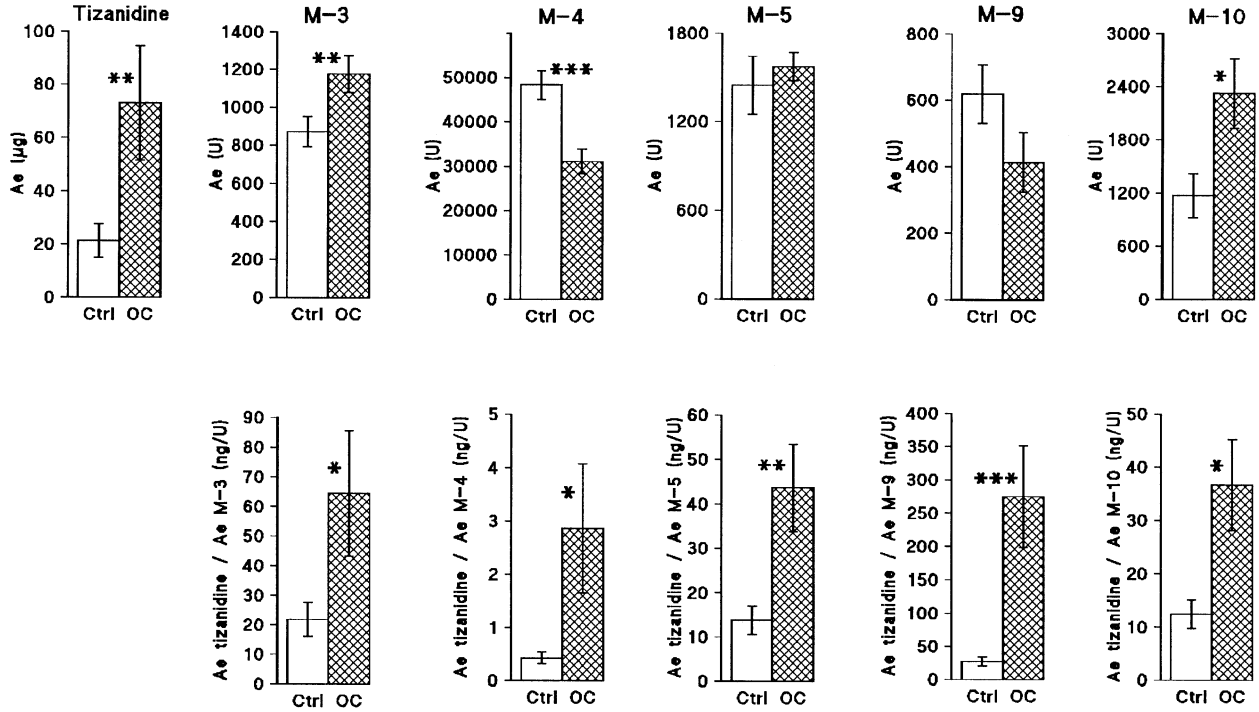


**Fig 5.** Amount excreted into urine within 24 hours (Ae) (mean ± SEM) of tizanidine, Ae of tizanidine metabolites M-3, M-4, M-5, M-9, and M-10, and urine tizanidine/metabolite ratios in 15 female control subjects (Ctrl) and 15 users of OCs after 4 mg tizanidine. *1 Asterisk*, $P < .05$; *2 asterisks*, $P < .01$; *3 asterisks*, $P < .001$.

3.0 times higher ($P < .001$) and the AUC(0-∞) was 3.9 times greater ($P < .001$), on average, in the OC users than in the control subjects, but there was no statistically significant difference in the $t_{½}$ or $t_{max}$ of tizanidine between the groups (Table I and Figs 2 and 3). The greatest individual value of tizanidine AUC(0-∞) in the OC group exceeded the mean AUC(0-∞) of tizanidine in the control group by nearly 20-fold and the greatest individual control tizanidine AUC(0-∞) value by nearly 10-fold (Fig 3). In the 3 subjects with a higher ethinyl estradiol dose (30 µg) in the OCs, the $C_{max}$ and AUC(0-∞) of tizanidine were similar to those in the other OC users (Fig 3).

***Tizanidine metabolites M-3 and M-4 in plasma.*** In the OC group the mean $t_{½}$ ($P < .001$) and $t_{max}$ ($P = .034$) of M-3 were longer and the AUC(0-∞) ($P = .017$) was greater than in the control group (Table I and Fig 4). The AUC(0-∞) ($P = .066$) and $C_{max}$ ($P = .005$) of M-4 were smaller in the OC users than in the control subjects. Furthermore, in the users of OCs, the mean plasma tizanidine/M-3 AUC(0-∞) ratio was 2.2 times higher ($P < .001$) and the mean plasma tizanidine/M-4 AUC(0-∞) ratio was 5.2 times higher ($P < .001$) than in the control subjects.

***Excretion of tizanidine and its metabolites into urine.*** The amount of unchanged tizanidine excreted in urine (Ae) was 3.8 times higher in the OC users than in the control subjects ($P = .008$), but there was no difference in its renal clearance between the groups (Table I and Fig 5). The Ae values for M-3 ($P = .006$) and M-10 ($P = .01$) were larger whereas the Ae of M-4 was smaller ($P < .001$) in the OC users than in the control subjects (Fig 5). However, all tizanidine/metabolite (M-3, M-4, M-5, M-9, and M-10) excretion ratios in urine were higher in the OC users than in the control subjects ($P < .05$).

***Pharmacodynamic variables.*** There were no statistically significant differences in pharmacodynamic variables between the groups at baseline. In the control subjects, tizanidine reduced the systolic and diastolic blood pressures from baseline values (mean of the maximal reductions) by −17 mm Hg and −13 mm Hg, respectively (Fig 6 and Table II). The corresponding reductions were significantly greater in the OC users; that is, −29 mm Hg ($P = .002$) and −21 mm Hg ($P = .009$), respectively. In addition, the subjective drug effect was stronger in the OC users ($P = .01$) than in the control subjects. The effects of tizanidine on heart

**Table I.** Pharmacokinetic variables of 4 mg tizanidine and its metabolites M-3 and M-4 in 15 users of oral contraceptives and 15 female control subjects

| *Variable* | *Control subjects* | *OC users* | *OC/control ratio and 95% CI* | *P value* |
|---|---|---|---|---|
| Tizanidine | | | | |
| $C_{max}$ (ng/mL) | 2.12 ± 1.43 | 6.40 ± 3.84 | 3.02 (2.01-5.79) | < .001 |
| $t_{max}$ (min) | 60 (40-180) | 60 (40-120) | | .60 |
| $t_{½}$ (h) | 1.35 ± 0.23 | 1.60 ± 0.52 | 1.18 (0.98-1.37) | .090 |
| AUC(0-∞) (ng · h/mL) | 6.27 ± 4.61 | 24.57 ± 26.46 | 3.92 (2.07-7.21) | < .001 |
| $CL_{renal\ 0\text{-}24}$ (L/h) | 3.48 ± 1.68 | 3.50 ± 1.44 | 1.01 (0.74-1.44) | .85 |
| M-3 | | | | |
| $C_{max}$ (U) | 0.85 ± 0.30 | 0.72 ± 0.19 | 0.84 (0.68-1.09) | .21 |
| $t_{max}$ (min) | 90 (40-240) | 120 (60-720) | | .034 |
| $t_{½}$ (h) | 4.18 ± 1.24 | 8.82 ± 6.07 | 2.11 (1.42-2.60) | < .001 |
| AUC(0-∞) (U · h/mL) | 5.32 ± 3.11 | 9.26 ± 7.20 | 1.74 (1.11-2.67) | .017 |
| AUC(0-∞) ratio (tizanidine/M-3) | 1.09 ± 0.39 | 2.42 ± 0.76 | 2.22 (1.68-3.00) | < .001 |
| M-4 | | | | |
| $C_{max}$ (U) | 1.55 ± 0.31 | 1.19 ± 0.33 | 0.77 (0.62-0.92) | .005 |
| $t_{max}$ (min) | 180 (60-240) | 180 (90-300) | | .25 |
| $t_{½}$ (h) | 4.52 ± 0.53 | 4.95 ± 1.23 | 1.10 (0.95-1.22) | .21 |
| AUC(0-∞) (U · h/mL) | 12.65 ± 3.09 | 10.54 ± 2.43 | 0.83 (0.69-1.01) | .066 |
| AUC(0-∞) ratio (tizanidine/M-4) | 0.52 ± 0.28 | 2.68 ± 2.62 | 5.15 (2.59-8.25) | < .001 |

Data are given as mean ± SD or mean and 95% CI, except for $t_{max}$ data, which are given as median and range.
OC, Oral contraceptives; CI, confidence interval; $C_{max}$, peak concentration in plasma; $t_{max}$, time to reach peak concentration in plasma; $t_{½}$, half-life; AUC(0-∞), area under plasma concentration–time curve from time 0 to infinity; $CL_{renal\ 0\text{-}24}$, renal clearance.

rate, subjective drowsiness, and Digit Symbol Substitution Test were not significantly different between the groups. However, the effect of tizanidine on all pharmacodynamic variables, except heart rate, correlated significantly with the plasma concentration of tizanidine (data not shown). For example, there was a significant correlation ($P < .001$) between the $C_{max}$ of tizanidine and the maximal decrease in systolic blood pressure (Fig 6, *B*).

***Caffeine test.*** The mean plasma caffeine/paraxanthine concentration ratio was 2.8 times higher in users of OCs (4.60 ± 2.56) than in the control subjects (1.62 ± 0.71) ($P < .001$).

***Correlations between tizanidine pharmacokinetics and caffeine/paraxanthine ratio.*** The caffeine/paraxanthine ratio correlated significantly with, for example, the AUC(0-∞), $C_{max}$, and Ae of tizanidine, as well as with the tizanidine/M-3 and tizanidine/M-4 AUC(0-∞) ratios (Table III and Fig 7). The subject who had the highest caffeine/paraxanthine ratio had, by far, the highest $C_{max}$ and AUC(0-∞) of tizanidine (Fig 3). The caffeine/paraxanthine ratio and the tizanidine AUC(0-∞) correlated strongly with the urinary tizanidine/metabolite (M-3, M-4, M-5, and M-9) Ae ratios, whereas the correlations with the tizanidine/M-10 Ae ratio were weaker (Table III).

## DISCUSSION

The mean $C_{max}$ and AUC(0-∞) values of tizanidine were considerably greater and its pharmacologic effects were stronger in the group of women using OCs than in the women without OCs. However, there was a large interindividual variation in the plasma tizanidine concentrations within both groups, and a fair amount of overlap occurred between the groups (Fig 3). The pharmacodynamic effects of tizanidine were greatly dependent on its plasma concentrations. Thus, for example, the maximal decrease in systolic blood pressure correlated well with the $C_{max}$ of tizanidine (Fig 6, *B*), demonstrating a similar overlap in both the pharmacodynamic and pharmacokinetic data. In any case the majority of the OC users had $C_{max}$ and AUC(0-∞) values that were higher than the highest values of the control subjects. It is noteworthy that there was no significant difference between the OC and control groups in the $t_{½}$ of tizanidine (Table I and Fig 3).

In vitro, gestodene is a potent inhibitor of CYP3A4,[2,6] but even at 100 μmol/L (ie, 10,000 times higher than the therapeutic concentration in plasma), it has had no effect on CYP1A2, as measured by phenacetin *O*-deethylation.[2] The effect of ethinyl estradiol on CYP1A2 activity has only been poorly investigated in vitro. However, CYP1A2 catalyzes the biotransfor-

mation of ethinyl estradiol to its main metabolite, 2-hydroxy–ethinyl estradiol.[31] In previous studies, OCs have reduced the clearance of theophylline, caffeine, and antipyrine by 30% to 55% in humans,[7,8,10,11,13] but the $C_{max}$ of caffeine or theophylline has remained unaffected.[7,10,11] The use of ethinyl estradiol (50 μg/d) has reduced caffeine clearance by 38%[32] and the combination of ethinyl estradiol (50 μg/d) and levonorgestrel (125 μg/d) by 34%.[32] In another study a combination of ethinyl estradiol (30 μg/d) and levonorgestrel (125 μg/d) or gestodene (75 μg) has reduced caffeine clearance by 54% and 55%, respectively.[11] On the other hand, the serum concentrations of selegiline have been 10 to 20 times higher in women using OCs containing ethinyl estradiol and gestodene or levonorgestrel compared with women without concomitant medications.[33] CYP1A2 metabolizes selegiline, at least partly, in humans.[34]

In our study the OC users had used the OC preparation for at least 1 complete cycle before the OC study cycle, and they had used OCs daily for 6 to 21 days immediately before the study day. Given that the half-lives of ethinyl estradiol and gestodene are on the order of 24 hours, the plasma concentrations of ethinyl estradiol and gestodene were close to the steady state on the study day.[35] However, because ethinyl estradiol induces the formation of sex hormone–binding globulin, to which gestodene binds, concentrations of total plasma gestodene can continue to increase for the whole cycle.[35,36] In any case there was no significant correlation (data not shown) between the day of OC use (ranging from 6 to 21 days) and the caffeine/paraxanthine ratio or the pharmacokinetic variables of tizanidine. In the 3 women who used a higher dose of ethinyl estradiol (30 μg compared with 20 μg in the other 12 OC users), the caffeine/paraxanthine ratios and tizanidine concentrations were not higher than in the other OC users (Fig 3). Furthermore, there were no differences in the extent of interaction between women using different brands of OCs (data not shown). There can be considerable interindividual differences in the plasma concentrations of both gestodene and ethinyl estradiol in OC users, governed mainly by genetic and acquired factors.[35] In addition, the time interval between the ingestion of OCs and tizanidine might have an effect on the extent of interaction. In our study, however, all OC users ingested tizanidine exactly 1 hour after the OC.

The caffeine/paraxanthine ratio reflects mainly systemic CYP1A2 activity, because caffeine, in contrast to tizanidine, lacks significant presystemic metabolism.[22,25] The mean caffeine/paraxanthine ratio was nearly 3 times higher in the users of OCs than in the control subjects, indicating a moderately strong inhibition of systemic CYP1A2 activity by OCs. For comparison, ciprofloxacin (500 mg twice daily) and fluvoxamine (100 mg/d) have increased caffeine/paraxanthine ratios by 2.1-fold and 12.5-fold, respectively.[22,23] Ciprofloxacin and fluvoxamine have increased the $C_{max}$ and AUC of tizanidine even more than did OCs in our study,[22,23] and only fluvoxamine has markedly increased the $t_{½}$ of tizanidine.[22] In the OC users the $C_{max}$ and AUC of tizanidine were higher than in the control subjects, but there was no significant difference between the groups in the $t_{½}$ of tizanidine, indicating that mainly the presystemic metabolism of tizanidine was affected by the OCs, with a minimal effect on its systemic elimination. It should be noted that the small, statistically nonsignificant (19%) increase in the mean $t_{½}$ was a result of 1 OC user with a long $t_{½}$ (Fig 3).

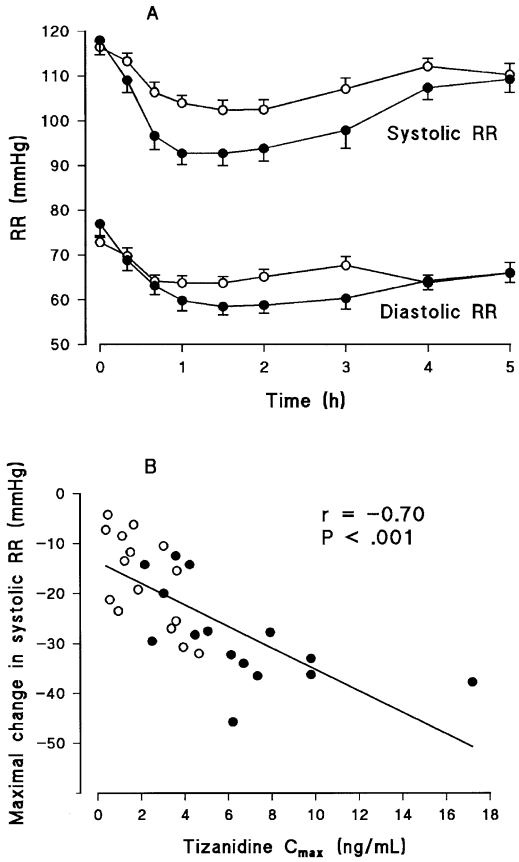


**Fig 6.** Mean (±SEM) systolic and diastolic blood pressure (RR) (**A**) and relationship between peak concentration of tizanidine in plasma ($C_{max}$) and maximal change in systolic RR from baseline value (**B**) in 15 users of OCs (*solid circles*) and 15 female control subjects (*open circles*) after 4 mg tizanidine.

**Table II.** Pharmacodynamic variables: Maximum changes from baseline values (minimum or maximum) and incremental/decremental AUC(0-12) for blood pressures, heart rate, and psychomotor tests (subjective drowsiness, subjective drug effect, and DSST) after 4 mg tizanidine in 15 users of oral contraceptives and 15 female control subjects

| *Variable* | *Control subjects* | *OC users* | *Difference between phases and 95% CI* | *P value* |
|---|---|---|---|---|
| Systolic blood pressure | | | | |
| Minimum (mm Hg) | −17 ± 9 | −29 ± 10 | −12 (−19 to −4) | .002 |
| Decremental AUC(0-12) (mm Hg · h) | −55 ± 90 | −111 ± 85 | −56 (−121 to 10) | .093 |
| Diastolic blood pressure | | | | |
| Minimum (mm Hg) | −13 ± 5 | −21 ± 8 | −7 (−12 to −29) | .009 |
| Decremental AUC(0-12) (mm Hg · h) | −73 ± 58 | −118 ± 85 | −46 (−100 to 9) | .10 |
| Heart rate | | | | |
| Minimum (beats/min) | −8 ± 5 | −9 ± 4 | 0 (−4 to 3) | .88 |
| Incremental AUC(0-12) (beats/min · h) | 59 ± 97 | 32 ± 78 | −27 (−93 to 39) | .41 |
| Drowsiness (VAS) | | | | |
| Maximum (mm) | 41 ± 19 | 56 ± 24 | 15 (−1 to 32) | .068 |
| Incremental AUC(0-12) (mm · h) | −18 ± 227 | 77 ± 188 | 95 (−61 to 251) | .22 |
| Drug effect (VAS) | | | | |
| Maximum (mm) | 31 ± 25 | 55 ± 23 | 24 (6 to 42) | .012 |
| Incremental AUC(0-12) (mm · h) | 75 ± 79 | 136 ± 88 | 61 (−2 to 124) | .057 |
| DSST | | | | |
| Minimum (symbols/2 min) | −58 ± 104 | −14 ± 9 | 44 (−11 to 99) | .11 |
| Decremental AUC(0-12) (symbols/2 min · h) | −36 ± 45 | −61 ± 61 | −25 (−65 to 15) | .22 |

Data are given as mean ± SD or mean and 95% CI.
AUC(0-12), Area under effect versus time curve from time 0 to 12 hours; VAS, visual analog scale; DSST, Digit Symbol Substitution Test.

Tizanidine is biotransformed to several metabolites (eg, M-3, M-4, M-5, M-9, and M-10), of which M-3 and M-4 are the main metabolites in plasma (Fig 1).[24] The excretion of M-3 into urine was greater whereas that of M-4 was smaller in the OC users than in control subjects. This can be explained by inhibition of the formation of M-4 from M-3 by the OCs, because the $t_{½}$ and AUC(0-∞) of M-3 were increased and the plasma concentrations of M-4 were reduced by the OCs. The CYP enzymes that are responsible for the formation of different metabolites are not known in detail, although tizanidine is metabolized mainly by CYP1A2.[22,23,37] The significant correlations between the caffeine/paraxanthine ratio or tizanidine AUC(0-∞) and the tizanidine/metabolite ratios in plasma (M-3 and M-4) (Fig 7, *B* and *C*, and Table III) and urine (M-3, M-4, M-5, and M-9) (Table III) suggest that CYP1A2 is important in the formation of the metabolites M-3, M-4, M-5, and M-9. However, because the correlation between the caffeine/paraxanthine ratio and the urine tizanidine/M-10 Ae ratio was weaker, CYP1A2 may not be crucial in the formation of the metabolite M-10. The tizanidine/metabolite ratios in plasma (M-3 and M-4) and urine (M-3, M-4, M-5, M-9, and M-10) were 2 to 10 times higher in the OC users than in the control subjects (Fig 5), consistent with inhibition of the formation of these metabolites by the OCs.

About 100 million women are using OCs for contraception. Thus concomitant use of tizanidine and OCs may not be uncommon in countries where tizanidine is in general use. The effects of OCs on tizanidine pharmacokinetics and pharmacodynamics are clinically significant as observed, for example, in the effects on blood pressure (Fig 6, *A*). Although the mean effects of OCs on tizanidine are not as strong as those of ciprofloxacin and fluvoxamine, which have increased tizanidine AUC by 10-fold and 33-fold and $C_{max}$ by 7-fold and 12-fold, respectively,[22,23] the effects can be alarmingly strong in certain subjects. In 1 of 15 healthy OC users, the AUC of tizanidine was nearly 20 times greater than the mean AUC in the control subjects, and her blood pressure fell from 111 mm Hg/74 mm Hg at baseline to 79 mm Hg/47 mm Hg with tizanidine. Thus, in an individual woman, the effect of OCs on the pharmacokinetics and pharmacodynamics of tizanidine can be much stronger than what could be inferred from

**Table III.** Correlations of caffeine/paraxanthine ratio and AUC(0-∞) of tizanidine with AUC(0-∞), $C_{max}$, and $t_{½}$ of tizanidine, tizanidine/M-3 and tizanidine/M-4 AUC(0-∞) ratios, amount of tizanidine excreted into urine, and tizanidine/metabolite (M-3, M-4, M-5, M-9, and M-10) ratios in urine after 4 mg tizanidine in 15 users of oral contraceptives and 15 female control subjects

| | *r Value** | |
|---|---|---|
| *Variable* | *Caffeine/paraxanthine ratio* | *Tizanidine AUC(0-∞)* |
| Tizanidine in plasma | | |
| AUC(0-∞) | 0.87 | |
| $C_{max}$ | 0.91 | 0.94 |
| $t_{½}$ | 0.73 | 0.86 |
| AUC(0-∞) ratio | | |
| Tizanidine/M-3 | 0.78 | 0.67 |
| Tizanidine/M-4 | 0.92 | 0.95 |
| Ae | | |
| Tizanidine | 0.87 | 0.96 |
| Ae ratio | | |
| Tizanidine/M-3 | 0.80 | 0.94 |
| Tizanidine/M-4 | 0.83 | 0.97 |
| Tizanidine/M-5 | 0.86 | 0.93 |
| Tizanidine/M-9 | 0.69 | 0.71 |

*r* Value, Correlation coefficient; Ae, amount excreted in urine within 24 hours.
**P* < .001 for all correlations except for tizanidine/M-10 Ae ratios (*P* < .01).

the tizanidine product information,[28] if a 50% reduction in tizanidine clearance by OCs is assumed. On the other hand, there was a significant variability in tizanidine pharmacokinetics within the 2 groups, as well as a fair amount of overlap between them, which makes prediction of individual tizanidine response difficult. Furthermore, it should be noted that the OC preparations used in this study contained ethinyl estradiol and gestodene; the findings cannot be directly generalized to OC products containing progestogens or estrogens other than those used in our study.

In conclusion, OCs containing gestodene and ethinyl estradiol can markedly increase the plasma concentration and effects of tizanidine, probably mainly by inhibiting its CYP1A2-mediated presystemic metabolism. Because the therapeutic range of tizanidine is narrow, care should be exercised when tizanidine is prescribed to OC users.

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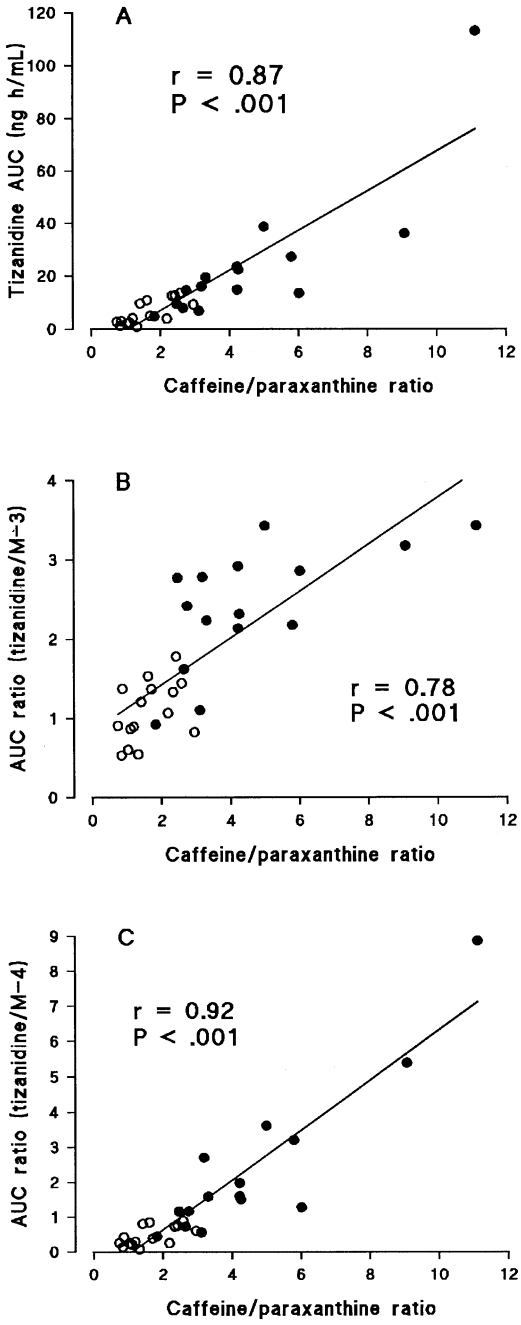


**Fig 7.** Relationships between plasma caffeine/paraxanthine ratio and tizanidine AUC(0-∞) (**A**), tizanidine/M-3 AUC(0-∞) ratio (**B**), and tizanidine/M-4 AUC(0-∞) ratio (**C**) in 15 users of OCs (*solid circles*) and 15 female control subjects (*open circles*) after 4 mg tizanidine.

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