Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2–mediated presystemic metabolism

Background and Objective: **Tizanidine, a centrally acting skeletal muscle relaxant, is metabolized mainly by cytochrome P450 (CYP) 1A2 and has a low oral bioavailability. The fluoroquinolone antibiotic ciprofloxacin is only a moderately potent inhibitor of CYP1A2. Our objective was to study the extent and mechanism of a possible interaction of ciprofloxacin with tizanidine.**

Methods: **In a double-blind, randomized, 2-phase crossover study, 10 healthy volunteers ingested 500 mg ciprofloxacin or placebo twice daily for 3 days. On day 3, a single dose of 4 mg tizanidine was ingested 1 hour after the morning dose of ciprofloxacin. Plasma concentrations of tizanidine and ciprofloxacin and pharmacodynamic variables were measured. A caffeine test was used as a marker for CYP1A2 activity.**

Results: **Ciprofloxacin increased the area under the plasma concentration–time curve from time 0 to infinity [AUC(0-∞)] of tizanidine by 10-fold (range, 6-fold to 24-fold; $P < .001$) and its peak concentration by 7-fold (range, 4-fold to 21-fold; $P < .001$), whereas its elimination half-life was only prolonged from 1.5 to 1.8 hours ($P = .007$). The pharmacodynamic effects of tizanidine were much stronger during the ciprofloxacin phase than during the placebo phase with regard to changes in systolic blood pressure (−35 mm Hg versus −15 mm Hg, $P = .001$), diastolic blood pressure (−24 mm Hg versus −11 mm Hg, $P < .001$), Digit Symbol Substitution Test ($P = .02$), subjective drug effect ($P = .002$), and subjective drowsiness ($P = .009$). The AUC(0-∞) of tizanidine and its change correlated ($P < .01$) with the caffeine/paraxanthine ratio and its change.**

Conclusions: **Ciprofloxacin greatly elevates plasma concentrations of tizanidine and dangerously potentiates its hypotensive and sedative effects, mainly by inhibiting its CYP1A2-mediated metabolism, at least when administered 1 hour before tizanidine. Tizanidine seems to be a useful probe drug for measuring presystemic metabolism by CYP1A2. Care should be exercised when tizanidine is used concomitantly with ciprofloxacin. (Clin Pharmacol Ther 2004;76:598-606.)**

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Tizanidine is a centrally acting skeletal muscle relaxant and α_2-adrenergic agonist.[1] It is prescribed for the symptomatic treatment of musculoskeletal pain associated with increased muscle tension, chronic spasticity, and chronic headache.[1,2] The oral bioavailability of tizanidine is low as a result of extensive first-pass metabolism.[3,4] Cytochrome P450 (CYP) 1A2 has been found to be the principal CYP enzyme involved in tizanidine metabolism in vitro.[5] In our recent study, fluvoxamine, a potent inhibitor of CYP1A2 and

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CYP2C19 and a moderate inhibitor of CYP3A4, CYP2C9, and CYP2D6, drastically increased plasma concentrations and effects of tizanidine.[6]

Ciprofloxacin, a widely used broad-spectrum fluoroquinolone antimicrobial agent, is a moderately potent and selective inhibitor of CYP1A2-mediated drug metabolism.[7,8] Ciprofloxacin has been found to impair the elimination of theophylline,[9,10] caffeine,[11] clozapine,[12] and ropivacaine.[13] In general, the extent of the interaction by ciprofloxacin has been considerably smaller than that caused by fluvoxamine; yet there seem to be no direct comparisons of their effects on orally administered CYP1A2 substrates, particularly on those with extensive first-pass metabolism. Ciprofloxacin, at a concentration approximately 30-fold higher than the peak plasma concentration in humans, inhibited the metabolism of tizanidine in human liver microsomes by only about 30%, whereas fluvoxamine, at therapeutic concentrations, had a strong inhibitory effect on tizanidine elimination.[5] Ciprofloxacin considerably differs from fluvoxamine with respect to its shorter half-life (3 to 4 hours versus 7 to 60 hours), better water solubility, and smaller extent of metabolism.[14] Therefore it was not possible to reliably predict the interaction potential of ciprofloxacin with orally administered tizanidine. Accordingly, a carefully controlled study was conducted in healthy subjects to explore the extent and mechanism of a possible interaction between ciprofloxacin and tizanidine, a CYP1A2 substrate with extensive presystemic metabolism.

METHODS

Subjects. Ten healthy male volunteers (age range, 22-28 years; weight range, 67-96 kg) participated in the study after giving written informed consent. Male subjects were chosen to avoid possible effects of menstrual cycle phases on tizanidine pharmacokinetics. The volunteers were ascertained to be healthy by medical history, physical examination, and routine laboratory tests before entering the study. 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.

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. A double-blind, randomized, 2-phase crossover study with a washout period of 3 weeks was carried out. The volunteers received 500 mg ciprofloxacin (two 250-mg Ciproxin tablets; Bayer, Leverkusen, Germany) or matched placebo twice daily at 8 AM and at 8 PM for 3 days. On day 3, after an overnight fast, a single oral dose of 4 mg tizanidine (one 4-mg Sirdalud tablet; Novartis Pharma, Wehr, Germany) was administered with 150 mL of water at 9 AM. A standard meal was served 3 and 7 hours after tizanidine ingestion. Drinking of grapefruit juice and tobacco smoking were not allowed for 1 week before each study day. Alcohol and drinks containing caffeine were not permitted on the study days.

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 and stored at −40°C until analysis.

The pharmacodynamic variables were assessed before administration of tizanidine and immediately after each blood sampling, up to 24 hours. The systolic and diastolic blood pressures and heart rate were measured twice from the forearm with the subject in a sitting position, and the mean value was used in the calculations. The blood pressures and heart rates were measured with an automatic oscillometric blood pressure monitor (HEM-711; Omron Healthcare, Hamburg, Germany). Before the study started, the volunteers were trained properly to perform 3 psychomotor tests.[15,16] In the Digit Symbol Substitution Test (DSST), the number of digits correctly substituted in 2 minutes was recorded, to measure the alertness of the participants. Subjective drowsiness and subjective overall drug effect were measured by use of 100-mm-long horizontal visual analog scales.

The subjects were under direct, close medical supervision during the days of administration of tizanidine. Fluids for intravenous infusion were available for immediate use, but they were not needed.

CYP1A2 activity assessment: Caffeine test. To evaluate the possible association between CYP1A2 activity and tizanidine pharmacokinetics, a caffeine test was performed on the second day of pretreatment during both phases.[17-19] 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) levels was taken from each subject 6 hours after caffeine intake.

Table I. Pharmacokinetic variables of 4 mg tizanidine in 10 healthy volunteers after pretreatment with 500 mg ciprofloxacin or placebo twice daily for 3 days

Variable	*Placebo phase (control)*	*Ciprofloxacin phase*	*Difference between phases and 95% CI*	*P value*
C_{max} (ng/mL)	1.2 ± 0.8	8.2 ± 2.6	7.0 (5.7 to 8.4)	<.001
% of control and range	100	664 (364 to 2080)		
t_{max} (min)	60 (40 to 120)	75 (40 to 120)		.6
$t_{½}$ (h)	1.5 ± 0.2	1.8 ± 0.3	0.3 (0.1 to 0.6)	.007
% of control and range	100	123 (94 to 147)		
AUC(0-∞) (ng · h/mL)	3.4 ± 2.3	33.1 ± 9.8	29.7 (23.6 to 35.8)	<.001
% of control and range	100	976 (563 to 2390)		

Data are given as mean ± SD or mean (95% CI), with t_{max} data given as median (range).
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.

Laboratory and statistical analyses. Plasma tizanidine concentrations were quantified by use of the PE SCIEX API 3000 liquid chromatography–tandem mass spectrometry system (Sciex Division of MDS Inc, Toronto, Ontario, Canada). Chromatography was performed on an XTerra RP C18 column (3.9 × 100 mm; Waters Corp, 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, and the ion transition monitored was mass-to-charge ratio (*m/z*) 254 to *m/z* 44. This transition represents the product ion of the $[M+H]^+$ ion. The limit of quantification for tizanidine was 0.02 ng/mL, and the day-to-day coefficients of variation (CV) were 6.0% at 0.1 ng/mL, 3.2% at 1.0 ng/mL, and 4.5% at 10 ng/mL (n = 6). Ciprofloxacin did not interfere with the determination of plasma tizanidine concentrations. The plasma concentrations of ciprofloxacin were determined by HPLC.[20] The limit of quantification was 0.1 mg/L, and the day-to-day CVs were 5.3% at 0.2 ng/mL and 1.0% at 6.0 ng/mL (n = 4). Plasma caffeine and paraxanthine concentrations were determined by HPLC, with β-hydroxyethyltheophylline used as the internal standard.[21,22] The day-to-day CV of caffeine and paraxanthine was less than 6% at relevant concentrations.

The pharmacokinetics of tizanidine was 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 ($t_{½}$). The terminal log-linear part of the concentration-time curve was visually identified for each subject. The elimination rate constant (k_e) was determined with the use of linear regression analysis of the log-linear part of the plasma concentration–time curve. The $t_{½}$ was calculated by the following equation: $t_{½} = \ln 2/k_e$. The AUC values were calculated by use of the linear trapezoidal rule for the rising phase of the tizanidine plasma concentration–time curve and the log-linear trapezoidal rule for the descending phase, with extrapolation to infinity, when appropriate, by division of the last measured concentration by k_e. The pharmacokinetics of ciprofloxacin was characterized by C_{max} and the AUC from 0 to 10 hours after the 8 AM dose of ciprofloxacin on day 3 [AUC(0-10)].

Results are expressed as mean ± SD. The pharmacokinetic and pharmacodynamic variables after the 2 pretreatments were compared by repeated-measures ANOVA with treatment sequence as a factor or, in the case of t_{max}, with the Wilcoxon signed rank test. For all variables except t_{max}, 95% confidence intervals (CIs) were calculated on the mean differences between the placebo and ciprofloxacin phases. The Pearson correlation coefficient was used to investigate possible relationships between the tizanidine and ciprofloxacin pharmacokinetic variables and the plasma caffeine/paraxanthine concentration ratio, as well as between the plasma concentrations of tizanidine and the pharmacodynamic variables measured. All data were analyzed with the statistical program Systat for Windows, version 6.0.1 (SPSS Inc, Chicago, Ill). The differences were considered statistically significant at $P < .05$.

RESULTS

Pharmacokinetics of tizanidine. Ciprofloxacin greatly raised the plasma concentrations of tizanidine (Table I and Fig 1). The mean AUC(0-∞) of tizanidine was increased to 980% ($P < .001$) and the peak concentration to 660% ($P < .001$) by ciprofloxacin compared with placebo. A large increase in the AUC(0-∞) (range,

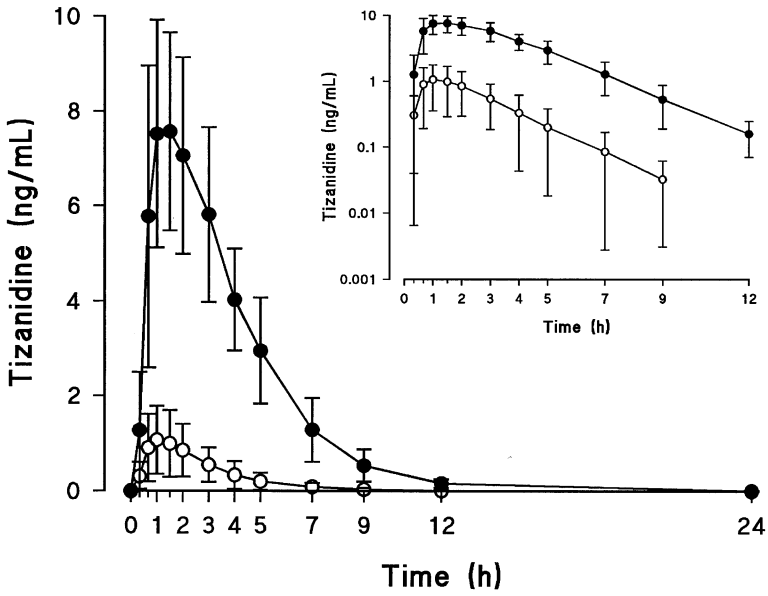

Fig 1. Mean (±SD) plasma concentrations of tizanidine in 10 healthy volunteers after single oral dose of 4 mg tizanidine, after treatment with placebo or 500 mg ciprofloxacin twice daily for 3 days. *Open circles,* Tizanidine during placebo; *solid circles,* tizanidine during ciprofloxacin. *Inset* depicts the same data on a semilogarithmic scale. Time 0 refers to administration of tizanidine (ie, 1 hour after the last dose of ciprofloxacin).

6-fold to 24-fold) and peak concentration (range, 4-fold to 21-fold) was seen in every subject (Fig 2). However, the mean elimination half-life of tizanidine was prolonged only slightly by ciprofloxacin (ie, from 1.5 to 1.8 hours; $P = .007$). The t_{max} of tizanidine was not changed significantly by ciprofloxacin.

Pharmacodynamics of tizanidine. The increased concentrations of plasma tizanidine during the ciprofloxacin phase were accompanied by much stronger pharmacodynamic effects than during the placebo phase (Table II and Fig 3). During the ciprofloxacin phase, the mean values (±SD) of the lowest systolic and diastolic blood pressure were 90 ± 9 mm Hg and 55 ± 7 mm Hg, respectively, which are considerably less than the corresponding mean values of the lowest blood pressures during the placebo phase (106 ± 6 mm Hg [$P < .001$] and 66 ± 4 mm Hg [$P < .001$]). In the ciprofloxacin phase the maximal decreases from baseline values in systolic and diastolic blood pressures (−35 ± 12 mm Hg and −24 ± 6 mm Hg, respectively) were greater than in the placebo phase (−15 ± 8 mm Hg [$P = .001$] and −11 ± 7 mm Hg [$P < .001$], respectively). In addition, in the ciprofloxacin phase the performance on the DSST was poorer ($P = .02$) and subjective drug effect ($P = .002$) and drowsiness ($P = .009$) were increased. There was no significant difference in heart rate between the 2 phases. The correlations between the plasma concentration of tizanidine and the change from baseline value in systolic blood pressure ($r = -0.78$) (Fig 4, *A*), diastolic blood pressure ($r = -0.72$), subjective drowsiness ($r = 0.56$), subjective drug effect ($r = 0.72$), and DSST ($r = -0.55$) were significant ($P < .001$).

Caffeine test. The plasma caffeine/paraxanthine ratio was 1.5 ± 0.5 in the placebo phase and 3.1 ± 1.7 in the ciprofloxacin phase; that is, ciprofloxacin increased the plasma caffeine/paraxanthine concentration ratio by 2.1-fold ($P = .005$). The AUC(0-∞) of tizanidine during the placebo phase correlated with the caffeine/paraxanthine ratio during the placebo phase ($r = 0.90$, $P < .001$) (Fig 4, *B*). In addition, the effect of ciprofloxacin on the AUC(0-∞) of tizanidine correlated with its effect on the caffeine/paraxanthine ratio ($r = 0.76$, $P = .008$) (Fig 4, *C*).

Concentrations of ciprofloxacin. The AUC(0-10) and C_{max} of ciprofloxacin were 7.8 ± 1.1 ng · h/mL and 1.4 ± 0.2 mg/L, respectively, and varied 1.6- and 1.5-fold between the individual subjects. There was a significant correlation between the AUC(0-10) of ciprofloxacin and the caffeine/paraxanthine ratio during the placebo phase ($r = 0.74$, $P = .01$).

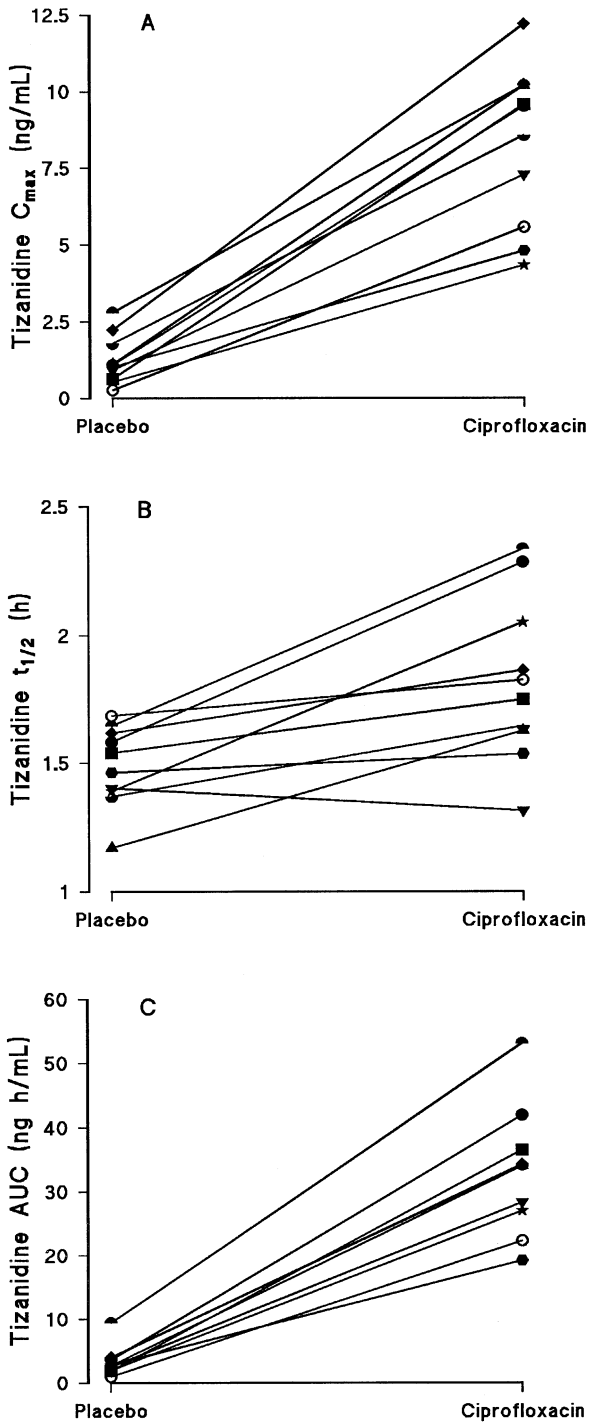

Fig 2. Individual values for peak concentration in plasma (C_{max}) (**A**), elimination half-life ($t_{½}$) (**B**), and area under plasma concentration–time curve from time 0 to infinity [AUC(0-∞)] (**C**) of tizanidine in 10 healthy volunteers after single oral dose of 4 mg tizanidine, after treatment with placebo or 500 mg ciprofloxacin twice daily for 3 days.

Adverse effects. All 10 subjects were somnolent and dizzy for about 3 hours after tizanidine intake during the ciprofloxacin phase. They had difficulties in fixating the eyes and concentrating on the psychomotor tests. Three of the subjects reported dryness of the mouth. These adverse effects were much milder or undetectable during the placebo phase.

DISCUSSION

Ciprofloxacin, at a usual dose of 500 mg twice daily, had a strong pharmacokinetic interaction with tizanidine. However, this interaction differed qualitatively and quantitatively from the recently described fluvoxamine-tizanidine interaction[6] and quantitatively from the previously published interactions of ciprofloxacin with other drugs.[9-13] Ciprofloxacin increased the AUC(0-∞) of tizanidine by 10-fold, in some subjects by up to 24-fold, and the C_{max} by 7-fold, but in contrast to the effect of fluvoxamine, the elimination half-life of tizanidine was prolonged only marginally. In previous reports, ciprofloxacin has only moderately (less than 2-fold) increased the AUC of other drugs that are metabolized by CYP1A2, including theophylline,[9,10] caffeine,[11] clozapine,[12] and ropivacaine.[13]

CYP1A2 is extensively expressed in the human liver and can also be expressed in some extrahepatic tissues, such as the gastrointestinal tract.[23] Tizanidine is metabolized mainly by CYP1A2, and ciprofloxacin even at high concentrations only moderately inhibits its elimination by human liver microsomes in vitro.[5] In this study significant correlations were found between the AUC(0-∞) of tizanidine and the caffeine test (an index of CYP1A2 activity) and their changes (Fig 4, *B* and *C*). However, the correlations between the $t_{½}$ of tizanidine and the caffeine test were not significant (data not shown). Thus CYP1A2 seems to be crucial in the presystemic metabolism of tizanidine, whereas other factors may also be important during the elimination phase.

The effect of ciprofloxacin on the caffeine/paraxanthine ratio was much weaker (2.1-fold increase) than that of fluvoxamine (13-fold increase) in our recent study.[6] Both ciprofloxacin and fluvoxamine greatly increased the AUC (10-fold and 33-fold) and C_{max} (7-fold and 12-fold) of tizanidine, but only fluvoxamine markedly prolonged its $t_{½}$ (from 1.5 to 4.3 hours by fluvoxamine versus from 1.5 to 1.8 hours by ciprofloxacin). Thus the effect of ciprofloxacin on the systemic elimination of tizanidine (and caffeine) was small, whereas its effect on the CYP1A2-mediated presystemic metabolism, reflected by the C_{max} and AUC of tizanidine, was considerable. The strong presystemic

Table II. Baseline values and effects of tizanidine on blood pressure, heart rate, and psychomotor tests during placebo and ciprofloxacin phases

Variable	*Placebo phase*	*Ciprofloxacin phase*	*Difference between phases and 95% CI*	*P value*
Systolic blood pressure (mm Hg)				
At baseline	122 ± 8	124 ± 7	3 (−3 to 8)	
Minimum after tizanidine	106 ± 6	90 ± 9	−17 (−24 to −10)	<.001
Diastolic blood pressure (mm Hg)				
At baseline	76 ± 7	78 ± 5	2 (−1 to 6)	
Minimum after tizanidine	66 ± 4	55 ± 7	−11 (−15 to −7)	<.001
Heart rate (beats/min)				
At baseline	54 ± 11	54 ± 11	0 (−5 to 5)	
Minimum after tizanidine	47 ± 8	48 ± 8	1 (−3 to 4)	.7
VAS: Drowsiness (mm)				
At baseline	44 ± 24	52 ± 13	8 (−12 to 27)	
Maximum after tizanidine	56 ± 19	82 ± 13	26 (9 to 43)	.009
VAS: Drug effect (mm)				
At baseline	0 ± 0	0 ± 0	0	
Maximum after tizanidine	8 ± 7	46 ± 27	38 (19 to 56)	.002
DSST (symbols/2 min)				
At baseline	104 ± 9	104 ± 10	1 (−1 to 3)	
Maximum after tizanidine	94 ± 9	86 ± 13	−8 (−15 to −2)	.02

Data are given as mean ± SD or mean and 95% CI.
VAS, Visual analog scale; DSST, Digit Symbol Substitution Test.

inhibition of CYP1A2 could be explained by the high concentrations of ciprofloxacin in the gastrointestinal wall and liver at the time of tizanidine ingestion (1 hour after ciprofloxacin). Consequently, the time interval between the ingestion of ciprofloxacin and tizanidine might affect the extent of interaction. The small effect of ciprofloxacin, compared with that of fluvoxamine, on the half-life of tizanidine and on the caffeine test can be a result of the shorter half-life of ciprofloxacin (3 to 4 hours versus 7 to 60 hours for fluvoxamine), as well as its smaller inhibitory potency for CYP1A2. Theoretically, the effect of fluvoxamine on CYP enzymes other than CYP1A2 could also contribute to its stronger effect on tizanidine pharmacokinetics.

The oral bioavailability of tizanidine in humans has been estimated to average 21% as a result of extensive first-pass metabolism.[4] According to the product information regarding Zanaflex (Elan Corporation, plc, Dublin, Ireland), the oral bioavailability of tizanidine is as high as 40%.[24] Yet the exact value is not known because tizanidine was not given intravenously.[4] The 7-fold increase in the C_{max} of tizanidine by ciprofloxacin in our current study and the previously reported 12-fold increase in tizanidine C_{max} by fluvoxamine[6] strongly suggest that the oral bioavailability of tizanidine averages less than 20%, probably about 10% to 15%, at least in young male subjects. Furthermore, there seems to be a considerable interindividual variation in the presystemic metabolism of tizanidine, which explains the large (more than 6-fold) range in the increases in the C_{max} and AUC of tizanidine by ciprofloxacin.

Tizanidine could be a sensitive probe drug for studying CYP1A2 activity in humans both under baseline conditions and after administration of potential inhibitors of CYP1A2. The C_{max} and AUC of tizanidine, a high-extraction drug, seem to (inversely) reflect mainly presystemic CYP1A2 activity. On the other hand, the clearance of caffeine, a drug with no presystemic metabolism,[25] reflects principally systemic elimination by CYP1A2. It would be interesting to compare tizanidine with other potential probes of CYP1A2 such as melatonin, which also has extensive presystemic metabolism.[26]

Ciprofloxacin is eliminated mainly in the unchanged form, with about 30% of the dose being metabolized. In this study there was a significant correlation between the AUC(0-10) of ciprofloxacin and the caffeine/paraxanthine ratio during the placebo phase. This finding suggests that CYP1A2 is also involved in the metabolism of ciprofloxacin.

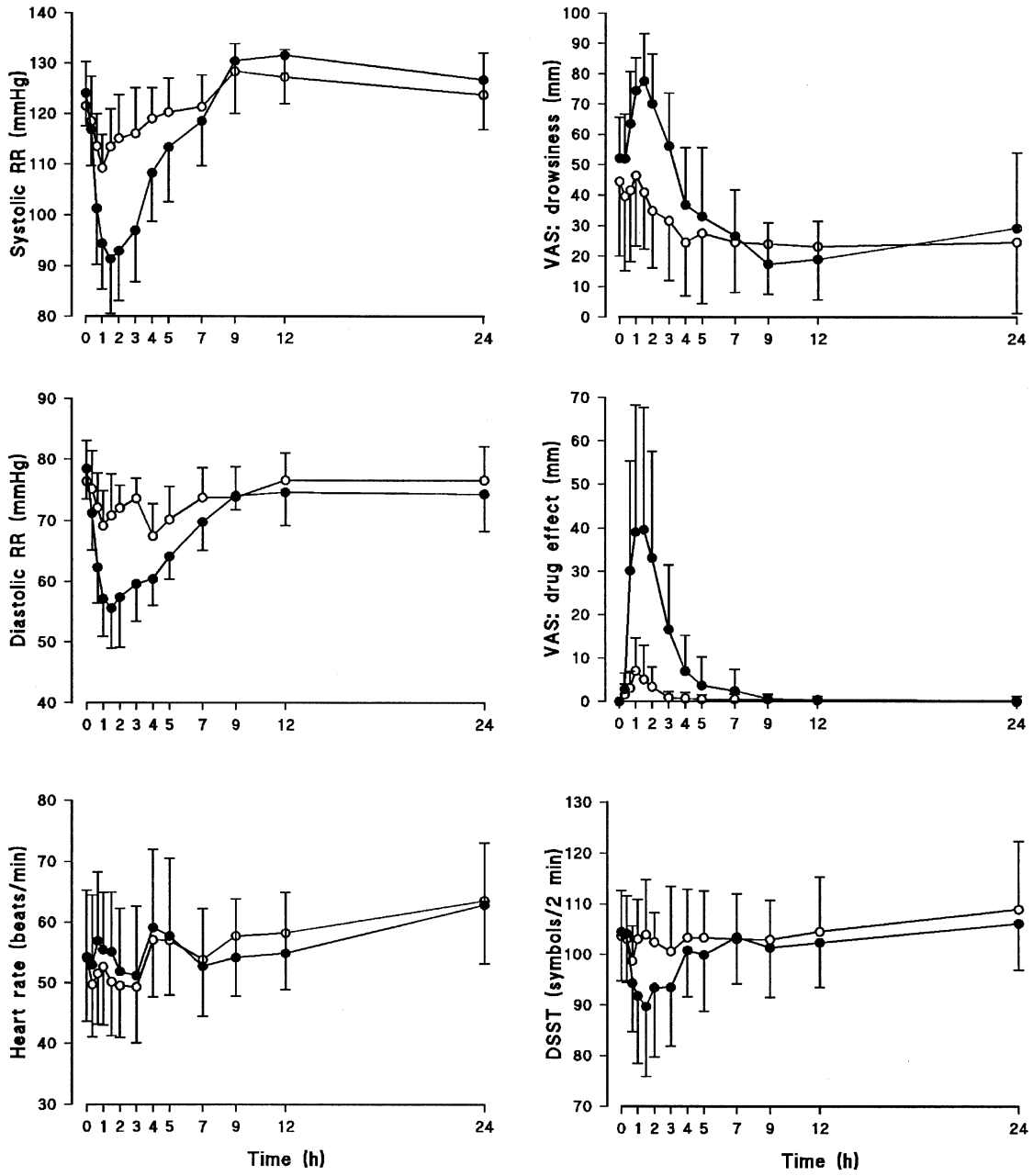

Fig 3. Mean ± SD systolic and diastolic blood pressure (RR) and heart rate values, recordings of subjective drowsiness and drug effect (visual analog scale [VAS]), and results of Digit Symbol Substitution Test (DSST) after 4-mg oral dose of tizanidine following pretreatment with placebo or 500 mg ciprofloxacin twice daily for 3 days. *Open circles,* Tizanidine during placebo; *solid circles,* tizanidine during ciprofloxacin.

During the ciprofloxacin phase, ingestion of 4 mg tizanidine resulted within 1 to 2 hours in significant hypotension, which lasted for hours and was not accompanied by compensatory tachycardia. In addition, the volunteers were somnolent and dizzy and their psychomotor performance was reduced for about 3 hours after tizanidine administration during the ciprofloxacin phase. Ciprofloxacin itself is not

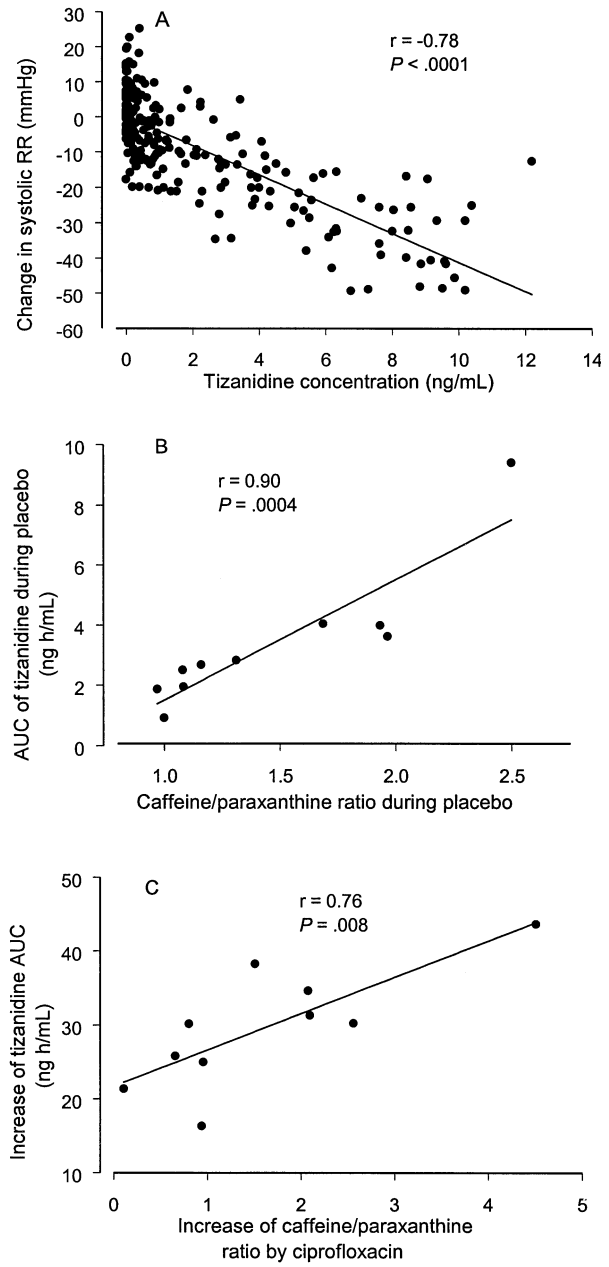

Fig 4. Relationship between plasma concentration of tizanidine and change from baseline in systolic blood pressure (**A**) and between AUC(0-∞) of tizanidine during placebo and caffeine/paraxanthine ratio during placebo (**B**), as well as between increase caused by ciprofloxacin in tizanidine AUC(0-∞) and increase caused by ciprofloxacin in caffeine/paraxanthine ratio (**C**).

known to lower blood pressure or to have a sedative effect. In this study it did not cause any significant changes in the pharmacodynamic variables at baseline before tizanidine administration. Thus it is obvious that the strong effects observed after the ingestion of tizanidine were caused by tizanidine and not by ciprofloxacin. This conclusion is also supported by the highly significant correlations between the plasma concentration of tizanidine and the changes from baseline in the blood pressures and other pharmacodynamic variables.

The therapeutic range of tizanidine is narrow. It should be noted that only a single 4-mg dose of tizanidine was administered in this study. Ingestion of tizanidine at higher doses, or twice or 3 times daily, could cause an even stronger interaction. During the ciprofloxacin phase, plasma concentrations of tizanidine 7 hours after dosing were at the same level as the peak tizanidine concentration during the control phase. The lowest systolic blood pressures were less than 80 mm Hg in some subjects after tizanidine ingestion during the ciprofloxacin phase. It is possible that the effects on blood pressure and psychomotor functions in elderly and infirm patients could be even greater. Further studies could reveal whether a tizanidine dose reduction, or dosing before or several hours after ciprofloxacin, would permit their concomitant use with an adequate margin of safety.

Both tizanidine and ciprofloxacin are commonly used drugs. For example, in Finland the daily consumption of tizanidine was 1.75 defined daily doses (DDD)/1000 inhabitants (DDD for tizanidine, 12 mg/d) and that of ciprofloxacin was 0.54 DDD/1000 inhabitants (DDD for ciprofloxacin, 1 g/d) during the year 2002.[27] In the United States the annual sales of tizanidine have been reported to exceed $200 million.[28] Thus it is possible that ciprofloxacin and tizanidine are also coadministered to patients in countries where both are in general use.

In conclusion, ciprofloxacin greatly raises the plasma concentrations of tizanidine and increases its concentration-dependent adverse effects, by inhibiting its CYP1A2-mediated presystemic metabolism. Clinicians should be aware that the interaction may have hazardous consequences, at least when tizanidine is administered simultaneously or shortly after ciprofloxacin. Tizanidine seems to be a sensitive probe drug for CYP1A2 activity studies in humans.

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References

1. Wagstaff AJ, Bryson HM. Tizanidine: a review of its pharmacology, clinical efficacy and tolerability in the

management of spasticity associated with cerebral and spinal disorders. Drugs 1997;53:435-52.
2. Lake AE III, Saper JR. Chronic headache. New advances in treatment strategies. Neurology 2002;59(Suppl 2):S8-S13.
3. Koch P, Hirst DR, von Wartburg BR. Biological fate of sirdalud in animals and man. Xenobiotica 1989;19:1255-65.
4. Tse FLS, Jaffe JM, Bhuta S. Pharmacokinetics of orally administered tizanidine in healthy volunteers. Fundam Clin Pharmacol 1987;1:479-88.
5. Granfors MT, Backman JT, Laitila J, Neuvonen PJ. Tizanidine is mainly metabolized by cytochrome P450 1A2 in vitro. Br J Clin Pharmacol 2004;57:349-53.
6. Granfors MT, Backman JT, Neuvonen M, Ahonen J, Neuvonen PJ. Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. Clin Pharmacol Ther 2004;75:331-41.
7. Davis R, Markham A, Balfour JA. Ciprofloxacin. An updated review of its pharmacology, therapeutic efficacy and tolerability. Drugs 1996;51:1019-74.
8. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet 1997;32:210-58.
9. Wijnands WJ, Vree TB, van Herwaarden CL. The influence of quinolone derivatives on theophylline clearance. Br J Clin Pharmacol 1986;22:677-83.
10. Batty KT, Davis TM, Ilett KF, Dusci LJ, Langton SR. The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects. Br J Clin Pharmacol 1995;39:305-11.
11. Harder S, Staib AH, Beer C, Papenburg A, Stille W, Shah PM. 4-Quinolones inhibit biotransformation of caffeine. Eur J Clin Pharmacol 1988;35:651-6.
12. Raaska K, Neuvonen PJ. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia. Eur J Clin Pharmacol 2000;56:585-9.
13. Jokinen MJ, Olkkola KT, Ahonen J, Neuvonen PJ. Effect of ciprofloxacin on the pharmacokinetics of ropivacaine. Eur J Clin Pharmacol 2003;58:653-7.
14. Dollery C. Therapeutic drugs. 2nd ed. Edinburgh (United Kingdom): Churchill Livingstone; 1999. p. C230, F139.
15. Backman JT, Olkkola KT, Neuvonen PJ. Rifampin drastically reduces plasma concentrations and effects of oral midazolam. Clin Pharmacol Ther 1996;59:7-13.
16. Olkkola KT, Backman JT, Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther 1994;55:481-5.
17. Kivistö KT, Wang J-S, Backman JT, Nyman L, Taavitsainen P, Anttila M, et al. Selegiline pharmacokinetics are unaffected by the CYP3A4 inhibitor itraconazole. Eur J Clin Pharmacol 2001;57:37-42.
18. Fuhr U, Rost KL, Engelhardt R, Sachs M, Liermann D, Belloc C, et al. Evaluation of caffeine as a test drug for CYP1A2, NAT2 and CYP2E1 phenotyping in man by in vivo versus in vitro correlations. Pharmacogenetics 1996;6:159-76.
19. Spigset O, Hägg S, Söderström E, Dahlqvist R. The paraxanthine:caffeine ratio in serum or in saliva as a measure of CYP1A2 activity: when should the sample be obtained? Pharmacogenetics 1999;9:409-12.
20. Maya MT, Goncalves NJ, Silva NB, Morais JA. Simple high-performance liquid chromatographic assay for the determination of ciprofloxacin in human plasma with ultraviolet detection. J Chromatogr B 2001;755:305-9.
21. Holland DT, Godfredsen KA, Page T, Connor JD. Simple high-performance liquid chromatography method for the simultaneous determination of serum caffeine and paraxanthine following rapid sample preparation. J Chromatogr B 1998;707:105-10.
22. Pickard CE, Stewart AD, Hartley R, Lucock MD. A rapid HPLC method for monitoring plasma levels of caffeine and theophylline using solid phase extraction columns. Ann Clin Biochem 1986;23:440-6.
23. Ding X, Kaminsky LS. Human extrahepatic cytochromes P450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. Annu Rev Pharmacol Toxicol 2003;43:149-73.
24. Product information for Zanaflex. Available from: URL: http://www.acorda.com/Zanaflex_Insert.pdf. Accessed Aug 7, 2004.
25. Dollery C. Therapeutic drugs. 2nd ed. Edinburgh (United Kingdom): Churchill Livingstone; 1999. p. C4.
26. Härtter S, Ursing C, Morita S, Tybring G, von Bahr C, Christensen M, et al. Orally given melatonin may serve as a probe drug for cytochrome P450 1A2 activity in vivo: a pilot study. Clin Pharmacol Ther 2001;70:10-6.
27. Finnish Statistics on Medicines 2002. Helsinki (Finland): National Agency for Medicines and Social Insurance Institution. 2003.
28. Biospace News. Available from: URL:http://www.biospace.com/news_story.cfm?StoryID=13914420&full=1. Accessed Aug 7, 2004.