Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers

Background: **Modafinil has been reported to produce a concentration-related induction of CYP3A4/5 activity in vitro in primary cultures of human hepatocytes.**
Objective: **Our objective was to determine whether the pharmacokinetics of steady-state ethinyl estradiol (INN, ethinylestradiol) and single-dose triazolam were altered after 4 weeks of modafinil treatment in volunteers.**
Methods: **This was a placebo-controlled, single-blind, single-period study in 41 female subjects who were receiving long-term treatment with an oral contraceptive that contained ethinyl estradiol (0.035 mg) and norgestimate (0.180-0.250 mg). Pharmacokinetic profiles for ethinyl estradiol and for a single oral dose of triazolam (0.125 mg) were obtained the day before initiation of treatment with modafinil (200 mg for 7 days, followed by 400 mg for 21 days) or placebo (28 days). A second dose of triazolam was administered with the final dose of modafinil, and pharmacokinetic profiling was repeated.**
Results: **The modafinil treatment group had a marked decrease in maximum observed plasma concentrations and areas under the plasma concentration–time curve for triazolam relative to placebo, with a much smaller decrease in these parameters for ethinyl estradiol. The half-life of triazolam was also decreased, but the half-life of ethinyl estradiol did not appear to be affected by treatment with modafinil.**
Conclusion: **Modafinil induced CYP3A4/5 activity in humans in vivo, suggesting that there is potential for metabolic drug-drug interactions between modafinil and substrates of CYP3A4/5. However, the induction appeared to be more gastrointestinal than hepatic in nature. Therefore significant metabolic drug-drug interactions are most likely to occur with compounds (such as triazolam) that undergo significant gastrointestinal CYP3A4/5-mediated first-pass metabolism. (Clin Pharmacol Ther 2002;71:46-56.)**

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Modafinil (*dl*-2-[(diphenylmethyl)sulfinyl]acetamide) (Provigil; Cephalon, Inc) is a novel wake-promoting agent that facilitates wakefulness in a variety of clinical models, including narcolepsy, obstructive sleep apnea, and perhaps shift work sleep disorder.[1-5] It is currently approved in the United States and in several other countries for treatment of excessive daytime sleepiness associated with narcolepsy.

Modafinil is readily absorbed,[6] with maximum plasma concentrations observed 2 to 4 hours after administration.[7] Its pharmacokinetics appear to be dose and time independent over a dose range from 200 to 600 mg, and its terminal half-life of modafinil after repeated administration is approximately 15 hours. Apparent pharmacokinetic steady state is achieved after 2 to 4 days of administration.[6,7] There are 2 circulating metabolites, modafinil acid and modafinil sulfone, but neither appears to contribute to the wakefulness-promoting action of modafinil.[7] The primary metabolic pathway in humans, amide hydrolysis, proceeds by way of esterase enzymes, but cytochrome P450 (CYP)

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Table I. Baseline characteristics of randomized subjects

Variable	*Group A (ethinyl estradiol–norgestimate + modafinil; n = 20)*	*Group B (ethinyl estradiol–norgestimate + placebo; n = 21)*
Age (y)		
Mean and SD	24.1 (5.9)	22.7 (4.5)
Range	19-42	19-35
Race		
White	n = 19 (95%)	n = 19 (90%)
Black	n = 1 (5%)	n = 2 (10%)
Height (in)		
Mean and SD	66.0 (2.1)	66.3 (2.2)
Range	62-70	62-71
Weight (lb)		
Mean and SD	145.9 (23.1)	153.8 (25.0)
Range	119-207	122-198
Frame size (n)		
Large	5 (25)	3 (14)
Medium	12 (60)	13 (62)
Small	3 (15)	5 (24)

enzymes have lesser contributions, through sulfur oxidation and phenyl ring hydroxylation.[7]

In clinical use, modafinil will be given concomitantly with other medications; therefore it is important to understand its effects on drug-metabolizing enzymes. In vitro, modafinil was found to have little or no capacity to inhibit the major CYP enzymes in human liver microsomes, except for CYP2C19, which was reversibly inhibited by modafinil with an inhibition constant (39 μmol/L) that approximated the steady-state maximum observed plasma concentration (C_{max}) observed when modafinil was administered as a 400-mg daily dose.[6,8] However, in primary cultures of human hepatocytes, incubation with modafinil (10 to 300 μmol/L) was found to induce CYP1A2, CYP2B6, and CYP3A4/5 activities and to suppress CYP2C9 activity in a generally concentration-related manner.[8] Of the CYP enzymes that were induced in vitro, CYP3A4/5 was considered to have the largest potential for drug-drug interactions as a result of its prevalence and its wide range of substrates.[9] In particular, the effectiveness of steroidal contraceptive agents that contained ethinyl estradiol (INN, ethinylestradiol) may be reduced by CYP3A4/5 induction, which would increase the rate of metabolic elimination and decrease the extent and duration of systemic exposure. Inducers of CYP3A4/5, such as rifampin (INN, rifampicin), phenobarbital, phenytoin, and carbamazepine, have been shown to promote the metabolic elimination of ethinyl estradiol, thereby increasing the incidence of contraceptive failure.[10-12]

This study was designed to examine the effect of repeated once-daily administration of modafinil at the highest approved dosage (ie, 400 mg) on the pharmacokinetic profile of ethinyl estradiol in healthy volunteers receiving Ortho Tri-Cyclen (Ortho-McNeil Pharmaceutical), a popular oral contraceptive that contains ethinyl estradiol and the progestin norgestimate. The extent of induction that would be produced at the lower recommended daily dosage (ie, 200 mg) is assumed to be equal to or less than that obtained at the higher dose.

However, because there is substantial intersubject and intrasubject variability in the pharmacokinetics of ethinyl estradiol[13,14] and because effects, if any, on the activity of conjugative enzymes may also affect blood levels of ethinyl estradiol,[10] single doses of triazolam (Halcion, Pharmacia), a commonly prescribed sedative hypnotic and anxiolytic agent, were also administered as an additional marker substrate for CYP3A4/5[15-17] to provide a more sensitive and specific assessment of the effect of modafinil on CYP3A4/5 activity.

METHODS

Subjects. Healthy female volunteers who were eligible for study participation provided informed written consent. Subjects (age range, 19-42 years) were required to be of childbearing potential, with the ability to document the use of the ethinyl estradiol and norgestimate combination product for at least 2 months. During the 4-week period of modafinil administration, subjects were required to use a medically accepted nonhormonal method of contraception as a supplement to ethinyl estradiol–norgestimate (eg, barrier method with spermicide or vasectomized partner); subjects agreed

Table II. Mean ± SD pharmacokinetic parameters for ethinyl estradiol*

	Group A (ethinyl estradiol–norgestimate + modafinil; n = 16)			*Group B (ethinyl estradiol–norgestimate + placebo; n = 18)*		
Parameter	*Cycle 2*	*Cycle 3*	Δ	*Cycle 2*	*Cycle 3*	Δ
AUC(0-τ) (pg · h/ml)	1175 ± 271	965 ± 532	–210 ± 451	1244 ± 333	1199 ± 366	–45 ± 231†
C_{max} (pg/ml)	151 ± 32	134 ± 52	–17 ± 39	151 ± 39	143 ± 38	–7 ± 26†
C_{trough} (pg/ml)	18.8 ± 7.3	15.8 ± 12.6	–2.9 ± 12.1	21.3 ± 8.2	21.2 ± 8.2	–0.2 ± 10.1
λ (h^{-1})	0.060 ± 0.014	0.059 ± 0.017	–0.002 ± 0.012	0.056 ± 0.012	0.055 ± 0.011	–0.001 ± 0.009
$t_{½}$ (h)	12.2 ± 2.9	13.1 ± 4.9	0.9 ± 3.9	13.0 ± 3.1	13.3 ± 2.8	0.2 ± 2.6
t_{max} (h)	1.3 ± 0.3	1.1 ± 0.3	–0.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	0.2 ± 0.5†

AUC(0-τ), Area under the plasma concentration–versus–time curve during 1 dosing interval; C_{max}, maximum observed plasma concentration; C_{trough}, minimum observed plasma concentration (24 hours after administration on pharmacokinetic sampling day); λ, terminal rate constant for elimination from plasma; $t_{½}$, terminal half-life; t_{max}, time when C_{max} was observed.

*Pharmacokinetic profiles for ethinyl estradiol were obtained on day 5, 6, or 7 in cycle 2 and on the last day of modafinil treatment in cycle 3.

†Statistically significant difference between treatment groups ($P < .05$).

to continue use of this method for a full menstrual cycle after completion of dosing with modafinil. Eligible subjects were required to have no current evidence of cervical dysplasia (as documented by a Papanicolaou test within the last year) and no clinically significant abnormal findings shown by physical examination, medical history, or clinical laboratory results at the screening visit. Subjects who were pregnant, nursing, or lactating and those who had received an injection of medroxyprogesterone acetate (Depo-Provera, Pharmacia) within 6 months of study initiation were excluded from the study. Placement or removal of levonorgestrel implants (Norplant; Wyeth-Ayerst Laboratories) within 90 days of study initiation also precluded study participation. Subjects were also required to be free of clinically significant disease or any condition that could jeopardize subject safety or study validity, as determined through their medical histories, physical examinations, and laboratory screenings. Use of tobacco products during the 12 months before the screening visit precluded study participation, as did treatment with agents known to cause alterations in hepatic drug-metabolizing enzyme activities (eg, barbiturates, phenothiazines, or cimetidine) within 30 days of the study.

Study design and procedures. This randomized, placebo-controlled, single-blind, single-period study was conducted by the clinical unit of MDS Harris (Lincoln, Neb) and followed a protocol approved by the MDS Harris Institutional Review Board. The study included a screening visit, followed by a treatment period that spanned 2 consecutive 28-day menstrual cycles (cycle 1 and cycle 2, respectively) and the first week of a third cycle (cycle 3). Treatment with ethinyl estradiol–norgestimate was maintained throughout the test period.

Subjects were randomly assigned to 1 of 2 treatment groups. On day 5, 6, or 7 of cycle 2 (Fig 1), subjects in group A received a single 0.125-mg dose of triazolam. Starting with the day after administration of single-dose triazolam (ie, day 6, 7, or 8 of cycle 2), group A subjects received once-daily 200-mg doses (2 100-mg tablets) of modafinil for 7 days, followed by once-daily 400-mg doses (4 100-mg tablets) for 21 days, taken with their daily ethinyl estradiol–norgestimate doses. The acclimatization period at 200 mg before initiation of treatment at the higher dosage was intended to lessen the potential for adverse events in this normal volunteer population. The potential for such benefit had been suggested by the lower incidence of withdrawals in the early portion of the second phase 3 study in patients with narcolepsy,[5] in which a dose step-up routine was used, relative to that in an earlier study,[4] in which there was no acclimatization period.

On the final day of modafinil treatment (ie, the same day of cycle 3 as their pharmacokinetic profiling day in cycle 2), subjects received a second 0.125-mg dose of triazolam with their scheduled doses of modafinil and ethinyl estradiol–norgestimate. Subjects randomized to group B followed the same treatment schedule as those in group A, but they received matching placebo in place of modafinil.

Study medications were taken with approximately 8 fluid ounces (240 ml) of room temperature tap water on an empty stomach at approximately the same time each morning during the entire treatment period. In addition, on the 2 days of pharmacokinetic profiling, the subjects fasted overnight (at least 10 hours) before administration and for approximately 4 hours after administration.

Subjects were admitted to the clinic on the evenings before the pharmacokinetic sampling days and were

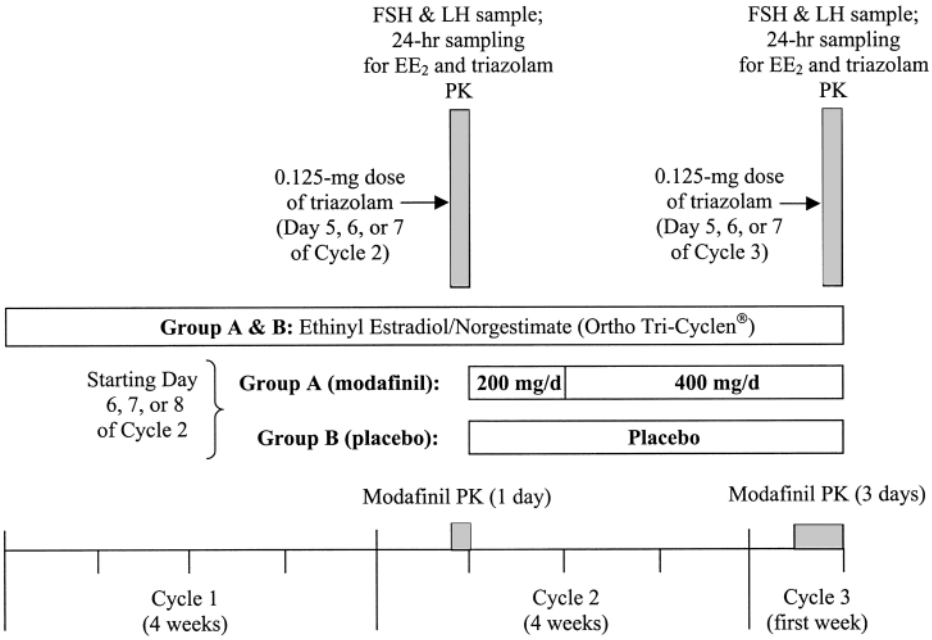

Fig 1. Diagrammatic representation of study procedures. EE_2, Ethinyl estradiol; PK, pharmacokinetics.

discharged after completion of the 24-hour plasma sampling period. Subjects participated as outpatients on all other days of the study. However, they were required to visit the clinic on the mornings of their 26th and 27th days of modafinil administration so that blood samples could be drawn for measurement of trough levels of ethinyl estradiol and of modafinil and its metabolites.

Compliance was checked during all visits after the initial dispensing of study medication. Compliance checks involved completion of study medication accountability reports and reviews of subject diaries. In addition, trough concentrations of ethinyl estradiol and of modafinil and its metabolites were measured in plasma samples obtained immediately before modafinil administration on the last 3 days of dosing with modafinil. Only the data from subjects who appeared to be at steady state were used in the pharmacokinetic analysis.

Blood samples (15 ml) were collected in Vacutainer blood-collecting tubes (Becton Dickinson & Co, Franklin Lakes, NJ) that contained lithium heparin immediately before study drug administration on the day of pharmacokinetic profiling in cycle 2 (day 5, 6, or 7) and at selected times (0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours) after dosing with ethinyl estradiol–norgestimate and triazolam on day 5, 6, or 7 in cycle 2 and after dosing with ethinyl estradiol–norgestimate, modafinil or placebo, and triazolam on the final day of treatment in cycle 3 (Fig 1). Additional predose blood samples were obtained on the 2 days before the second day of pharmacokinetic profiling. Along with a predose sample on the final day, these were used to ensure that modafinil and its metabolites had reached an apparent steady state. Blood samples were placed immediately in an ice bath, and plasma was harvested by means of low-speed centrifugation (approximately 2500 rpm) for 15 minutes at 4°C. Plasma was stored frozen (–20°C or less) in polypropylene tubes until analysis.

Plasma concentrations of ethinyl estradiol (PPD Development, Richmond, Va) were determined with use of gas chromatography coupled with tandem mass spectrometry. 17α-Ethinyl estradiol and its isotopically labeled internal standard (17α-ethinyl estradiol-$^{13}C_2$) were isolated from 1.0-ml aliquots of plasma by liquid-liquid extraction with use of a mixture of hexane–ethyl acetate (90:10). The organic layer was separated and evaporated to dryness under nitrogen. Sample extracts were derivatized with use of a combination of fluorinated acylating and fluorinated silylating reagents in pyridine. After derivatization, the sample extracts were purified by solid-phase extraction with aminopropyl cartridges, the eluants were evaporated to dryness under nitrogen, and the sample extracts were reconstituted in 1-decene. The derivatized extracts were stored at –20°C pending analysis.

Analysis was conducted with use of a Finnigan MAT SSQ700/7000 model gas chromatography–mass spectrometry system (Thermo Finnigan, San Jose, Calif) with negative ion chemical ionization with methane as the reagent gas and detected by means of selective ion monitoring. The analytes were chromatographically separated from endogenous compounds with a J&W Scientific DB-17HT fused silica capillary column (0.32 mm × 20 m). The approximate retention time for 17α-ethinyl estradiol was 6.3 minutes. This assay was validated with a quantitation range from 2.00 to 1000 pg/ml. Concentrations of norgestimate, the progestin component of Ortho Tri-Cyclen, were not measured in this study because the predominant initial metabolic reaction of norgestimate is not CYP mediated.[18,19]

Plasma concentrations of triazolam (Covance Laboratories, Madison, Wis) were determined with use of HPLC coupled with tandem mass spectrometry. Triazolam and the internal standard alprazolam were extracted from 0.2 ml of human plasma with a mixture of hexane and dichloromethane. After separation of the organic layer, the solvent was evaporated under nitrogen at 40°C, and the residue was reconstituted in acetonitrile. Separation was achieved on an Inertsil Silica, 50 × 2 mm, 5 μm column (Keystone Scientific, Inc, Bellefonte, Pa) with an acidified aqueous acetonitrile mobile phase. Separation of analyte and internal standard was achieved in less than 3 minutes. Detection was achieved by use of a Sciex API 3000+ instrument (MDS Sciex, Concord, Ontario, Canada) with mass selective detection in multiple reaction monitoring mode. The validated range of quantitation extended from 0.100 to 50.0 ng/ml.

Modafinil, modafinil acid, and modafinil sulfone were determined (Covance Laboratories) by use of a validated HPLC method with ultraviolet detection.[6] The quantifiable range for each of these 3 analytes was 0.100 to 20 μg/ml (0.200 ml plasma).

For pharmacodynamic analyses, 10-ml blood samples were collected immediately before study drug administration on the 2 days of 24-hour pharmacokinetic profiling (ie, on day 5, 6, or 7 in cycle 2 and on the last day of dosing in cycle 3). Plasma was prepared and levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were determined.

Adverse events were recorded at each clinic visit and concomitant medications were monitored. Blood and urine samples were collected for clinical laboratory testing (ie, hematologic testing, serum chemical testing, and urinalysis) at the screening visit, on the days before pharmacokinetic profiling, and at the conclusion of the study. On the first day of study drug administration, a 5-ml blood sample was collected for pregnancy testing. Physical examinations and 12-lead electrocardiograms were conducted at the screening visit, before the final administration of study medication, and 24 hours thereafter at the conclusion of the study. Vital signs, including sitting systolic and diastolic blood pressures and pulse rates, were obtained at the screening visit, before study drug administration on the 2 days of pharmacokinetic profiling, before study drug administration on the 2 consecutive days before the second pharmacokinetic profiling, and at selected times up to 24 hours after administration on the 2 days of pharmacokinetic profiling.

Pharmacokinetic analysis. Pharmacokinetic parameters for ethinyl estradiol, triazolam, modafinil, modafinil acid, and modafinil sulfone were estimated by use of noncompartmental methods[20] with WinNonlin™ software (professional version 2.1, 1997; Scientific Consulting Inc, Palo Alto, Calif). The C_{max} and minimum observed plasma concentration (C_{trough}) were obtained during the steady-state sampling intervals for ethinyl estradiol, modafinil, modafinil acid, and modafinil sulfone, and C_{max} was obtained for triazolam. The time corresponding to the appearance of C_{max} (t_{max}) was obtained without interpolation. The elimination half-life ($t_{½}$) for all compounds was calculated as $\ln(2)/\lambda$, with λ, the terminal rate constant for elimination from plasma, determined by linear regression analysis of at least 3 points on the terminal portion of semilogarithmic plasma concentration–versus–time curves. The linear trapezoidal rule was used to calculate the area under the plasma concentration–versus–time curve during the sampling interval [AUC(0-τ)] for ethinyl estradiol and the modafinil compounds and the AUC from time zero to the last measurable time point [AUC(0-τ)] for triazolam. The area under the concentration–time curve from time zero to infinity [AUC(0-∞)] for a single dose of triazolam was calculated as the sum of AUC(0-t) and the area extrapolated from the last measurable time point to infinity (C_{last}/λ).

Statistical analysis. Demographic variables for all randomized subjects were summarized with descriptive statistics. The Wilcoxon rank sum test and the χ^2 test were used to detect between-group differences in continuous (ie, age, baseline height, and weight) and categoric (ie, race, sex, and frame size) variables, respectively.

Data from all subjects who completed the study and were at steady state with respect to ethinyl estradiol and modafinil (the latter condition applied to group A only) were included in the pharmacokinetic and pharmacodynamic analyses. Descriptive statistical summaries of pharmacokinetic parameters for ethinyl estradiol, tria-

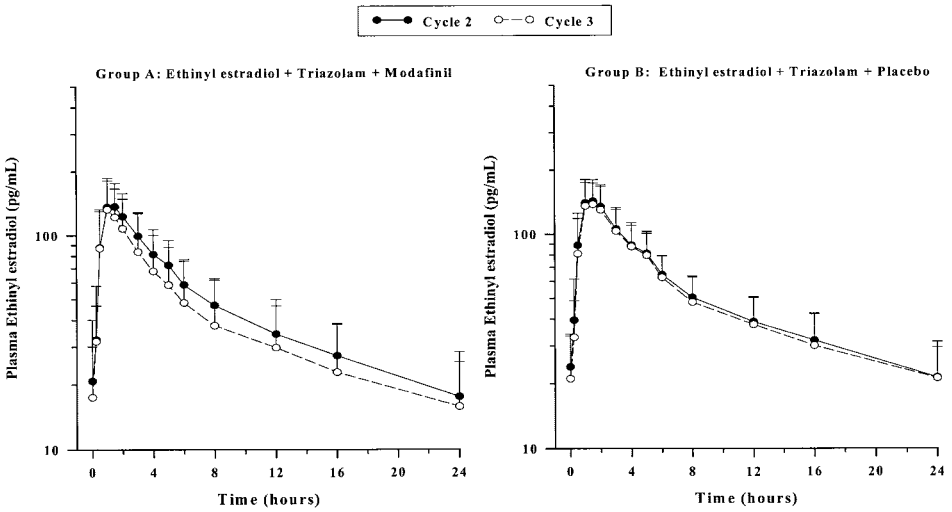

Fig 2. Mean plasma concentration–versus–time profiles for ethinyl estradiol before initiation of treatment (cycle 2) and on last day of 4 weeks of treatment (cycle 3) with modafinil (group A) or placebo (group B). Initial profiling was conducted on day 5, 6, or 7 of the first week of a standard dosing cycle (cycle 2) with Ortho Tri-Cyclen, which contains ethinyl estradiol (0.035 mg) and norgestimate (0.180 to 0.250 mg). Administration of modafinil (200 mg once daily for 1 week, followed by 400 mg once daily for 3 weeks) or matching placebo, began on the next day (day 6, 7, or 8) and continued for 4 weeks.

zolam, modafinil, modafinil acid, and modafinil sulfone were prepared by treatment group. The primary study parameters were the AUC(0-τ) for ethinyl estradiol and the AUC(0-∞) for triazolam. Secondary parameters for ethinyl estradiol included C_{max}, C_{trough}, t_{max}, λ, and $t_{½}$; secondary parameters for triazolam included the AUC(0-t), C_{max}, t_{max}, λ, and $t_{½}$. For modafinil, modafinil acid, and modafinil sulfone, pharmacokinetic parameters included the AUC(0-τ), C_{max}, C_{trough}, t_{max}, and, when calculable, λ and $t_{½}$. Between treatment groups, possible drug interactions were analyzed by comparison of the mean change in pharmacokinetic parameters for ethinyl estradiol and triazolam from the first to last pharmacokinetic profile (ie, from cycle 2 to cycle 3) with the Wilcoxon rank sum test. The Wilcoxon rank sum test also was used to compare between-group changes in levels of FSH and LH from cycle 2 to cycle 3.

All subjects who received at least 1 dose of study medication were included in the safety analysis. Adverse events were summarized for the 2 study periods: the ethinyl estradiol–norgestimate treatment period (beginning with day 1 of cycle 1 and ending the day before the first administration of modafinil or placebo on day 6, 7, or 8 of cycle 2) and the ethinyl estradiol–norgestimate plus modafinil–placebo treatment period (beginning with the first administration of modafinil or placebo on days 6, 7, or 8 of cycle 2 and continuing until the end of the study). Adverse events were tabulated by treatment group, body system, type of event, relationship to study drug, and severity. Clinical laboratory and vital sign data were summarized by use of descriptive statistics; changes from baseline in laboratory and vital sign parameters were summarized by treatment group.

RESULTS

Subjects. A total of 41 women were enrolled in the study and randomized to treatment. Sixteen of 20 subjects (80%) in group A and 18 of 21 subjects (86%) in group B completed the study and were evaluable for pharmacokinetic analyses. One subject in group A withdrew because of adverse events, 1 subject in each treatment group failed to meet entrance requirements at inpatient visits, 1 subject in each treatment group withdrew for personal reasons, and the remaining subjects withdrew for other reasons. There were no statistically significant differences between the treatment groups in the demographic and baseline characteristics of the randomized subjects (Table I).

Pharmacokinetics of ethinyl estradiol. A statistically significant difference was shown between treatment groups in the mean change from cycle 2 to cycle 3 in the AUC(0-τ) of ethinyl estradiol (P = .0044),

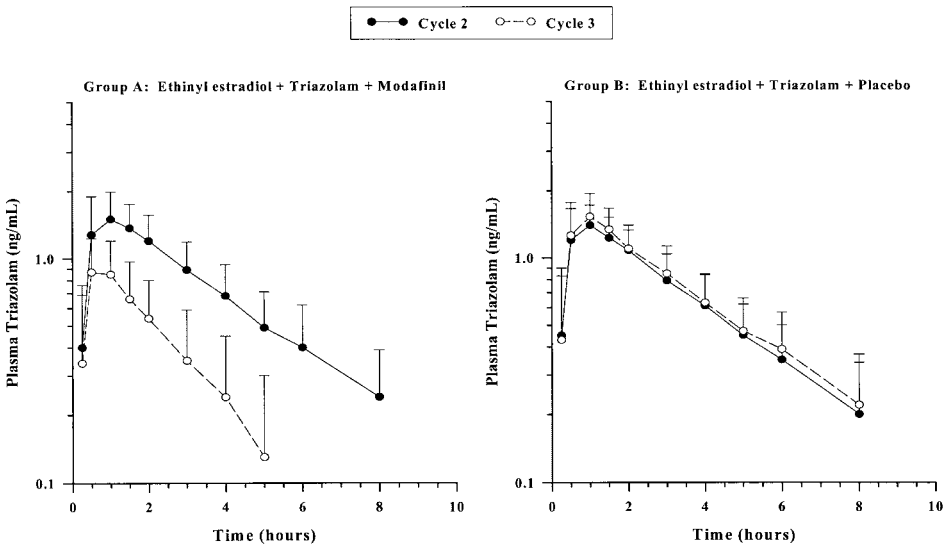

Fig 3. Mean plasma concentration–versus–time profiles for triazolam before initiation of treatment (cycle 2) and on last day of 4 weeks of treatment (cycle 3) with modafinil (group A) or placebo (group B). A single dose of triazolam (0.125 mg) was administered on each day of pharmacokinetic profiling. Administration of modafinil (200 mg once daily for 1 week, followed by 400 mg once daily for 3 weeks) began on the day after the initial profiling and continued for 4 weeks.

which was one of the primary pharmacokinetic parameters in the study (Table II; Fig 2). The mean AUC(0-τ) decreased by 18% in subjects receiving modafinil compared with a 4% decrease in subjects receiving placebo. In addition, there were statistically significant between-group differences in the mean change from cycle 2 to cycle 3 in C_{max} ($P = .032$) and t_{max} ($P = .013$). The mean C_{max} decreased by 11% in subjects receiving modafinil compared with a 5% decrease in subjects receiving placebo. The λ decreased by 3% and 2% in subjects receiving modafinil and placebo, respectively. The oral clearance (CL/F) was not included as a pharmacokinetic test parameter in the study protocol, although the values were calculated. In the modafinil-treated group, mean CL/F increased from 523.2 ± 126.8 ml/min to 720.6 ± 280.0 ml/min after the 4 weeks of treatment. In the placebo group, mean CL/F changed only minimally, from 500.8 ± 129.9 ml/min to 531.0 ± 164.6 ml/min.

Pharmacokinetics of triazolam. A statistically significant difference was shown between treatment groups in the mean change from cycle 2 to cycle 3 in the AUC(0-∞) of triazolam ($P < .0001$), which was one of the primary pharmacokinetic parameters in the study (Table III; Fig 3). The mean AUC(0-∞) decreased by 59% in subjects receiving modafinil compared with an 8% increase in subjects receiving placebo. Statistically significant between-group differences in the mean changes from cycle 2 to cycle 3 in all secondary triazolam pharmacokinetic parameters were also shown (all $P < .0001$), with the single exception of t_{max} ($P = .0736$). In particular, the mean C_{max} decreased by 42% in subjects receiving modafinil compared with a 7% increase in subjects receiving placebo. The λ increased by 51% in subjects receiving modafinil and decreased by 4% in subjects receiving placebo ($P < .0001$). The $t_{1/2}$ decreased by 35% in subjects receiving modafinil compared with a 4% increase in subjects receiving placebo. The CL/F was not included as a pharmacokinetic test parameter in the study protocol; however, the values were calculated. In the modafinil-treated group, mean CL/F increased from 369.0 ± 200.2 ml/min to 1008.2 ± 549.9 ml/min after the 4 weeks of treatment. In the placebo group, mean CL/F changed only minimally, from 374.2 ± 102.3 ml/min to 355.7 ± 119.1 ml/min.

Pharmacokinetics of modafinil, modafinil acid, and modafinil sulfone. The mean pharmacokinetic parameters for modafinil, modafinil acid, and modafinil sulfone obtained during cycle 3 from subjects in group A are presented in Table IV. The pharmacokinetic parameters obtained for modafinil and modafinil acid were consistent with those reported in a repeated-dose pharmacokinetic study of modafinil conducted previously.[6]

Table III. Mean ± SD pharmacokinetic parameters for triazolam*

	Group A (ethinyl estradiol–norgestimate plus modafinil; n = 16)			*Group B (ethinyl estradiol–norgestimate plus placebo; n = 18)*		
Parameter	*Cycle 2*	*Cycle 3*	Δ	*Cycle 2*	*Cycle 3*	Δ
AUC(0-∞) (ng · h/ml)	6.9 ± 2.7	2.8 ± 1.7	–4.1 ± 2.4	6.1 ± 2.2	6.6 ± 2.6	0.5 ± 1.4†
AUC(0-t) (ng · h/ml)	6.3 ± 2.6	2.4 ± 1.5	–3.9 ± 2.2	5.5 ± 2.0	6.0 ± 2.5	0.5 ± 1.5†
C_{max} (ng/ml)	1.6 ± 0.5	0.9 ± 0.4	–0.7 ± 0.4	1.5 ± 0.4	1.6 ± 0.4	0.1 ± 0.4†
λ (h^{-1})	0.29 ± 0.10	0.44 ± 0.13	0.15 ± 0.09	0.29 ± 0.06	0.28 ± 0.06	–0.01 ± 0.03†
$t_{½}$ (h)	2.6 ± 0.8	1.7 ± 0.6	–0.9 ± 0.6	2.5 ± 0.7	2.7 ± 0.7	0.1 ± 0.3†
t_{max} (h)	1.0 ± 0.4	0.7 ± 0.3	–0.3 ± 0.5	0.9 ± 0.3	0.9 ± 0.3	0.0 ± 0.4

AUC(0-∞), Area under the plasma concentration–versus–time curve from time zero to infinity for the single dose; AUC(0-t), area under the plasma concentration–versus–time curve from time zero to the last measurable time point; C_{max}, maximum observed plasma concentration; λ, terminal rate constant for elimination from plasma; $t_{½}$ terminal half-life; t_{max}, time when C_{max} was observed.
*Pharmacokinetic profiles for triazolam were obtained on day 5, 6, or 7 in cycle 2 and on the last day of modafinil treatment in cycle 3.
†Statistically significant difference between treatment groups, $P < .0001$.

Table IV. Mean ± SD pharmacokinetic parameters for modafinil, modafinil acid, and modafinil sulfone*

	*Group A (ethinyl estradiol–norgestimate plus modafinil; n = 13)**		
Parameter	*Modafinil*	*Modafinil acid*	*Modafinil sulfone*
AUC(0-τ) (μg · h/ml)	131 ± 27	51 ± 11	105 ± 69
C_{max} (μg/ml)	13.4 ± 2.4	6.1 ± 1.6	5.2 ± 3.1
C_{trough} (μg/ml)	2.4 ± 0.6	0.4 ± 0.1	4.3 ± 2.9
λ (h^{-1})	0.062 ± 0.011	0.128 ± 0.017	—
$t_{½}$ (h)	11.4 ± 1.9	5.5 ± 0.7	—
t_{max} (h)	1.8 ± 0.6	2.8 ± 0.8	4.8 ± 2.9

AUC(0-τ), Area under the plasma concentration–versus–time curve during 1 dosing interval; C_{trough}, minimum observed plasma concentration (predose on second pharmacokinetic sampling day); λ, terminal rate constant for elimination from plasma; $t_{½}$, terminal half-life; t_{max}, time when C_{max} was observed.
*Pharmacokinetic profiles of modafinil, modafinil acid, and modafinil sulfone in group A subjects were obtained on the last day of modafinil treatment in cycle 3.

Pharmacodynamics. No significant differences were noted between treatment groups in the mean changes from cycle 2 to cycle 3 in the mean plasma concentrations of FSH and LH (Table V). At the end of the study, mean (±SD) plasma concentrations of FSH increased by 0.4 ± 2.3 mIU/L in subjects receiving modafinil and by 0.1 ± 1.6 mIU/L in subjects receiving placebo. Mean (±SD) plasma concentrations of LH increased by 0.4 ± 4.9 mIU/L in subjects receiving modafinil and by 0.2 ± 3.7 mIU/L in subjects receiving placebo.

Safety assessment. All adverse events experienced by subjects receiving modafinil (group A) and all but 2 adverse events experienced by subjects receiving placebo (group B) were considered to be mild or moderate in nature. One subject in group A withdrew from the study while receiving modafinil because of mild abdominal pain that was considered to be unrelated to study medication. No subjects in group B withdrew because of adverse events. No serious adverse events or deaths were reported.

The most common treatment-emergent adverse events that occurred in 15% or more of subjects are presented by treatment period in Table VI. During the period that subjects received only ethinyl estradiol–norgestimate, the most commonly reported adverse event was headache (group A, 14 of 20 subjects [70%]; group B, 11 of 21 subjects [52%]). Overall, the incidence of adverse events in the ethinyl estradiol–norgestimate treatment period was not appreciably different between the 2 treatment groups.

Headache was also the most frequently reported adverse event during the treatment period in which subjects received ethinyl estradiol–norgestimate plus modafinil or placebo (group A, 13 of 18 subjects [72%]; group B, 10 of 19 subjects [53%]; Table VI). Overall, the incidence of adverse events was similar between the treatment groups. Adverse events that were considered to be related to study medication by the investigator and that occurred in at least 15% of subjects in group A were headache, asthenia, nausea, dizziness, metrorrha-

Table V. Mean ± SD plasma concentrations of FSH and LH*

Treatment group	*Hormone levels (mIU/L)*		
	Cycle 2	*Cycle 3*	Δ
FSH			
Group A (ethinyl estradiol–norgestimate plus modafinil; n = 16)	4.2 ± 1.8	4.6 ± 2.1	0.4 ± 2.3
Group B (ethinyl estradiol–norgestimate plus placebo; n = 18)	3.3 ± 1.6	3.5 ± 2.1	0.1 ± 1.6
LH			
Group A (ethinyl estradiol–norgestimate plus modafinil; n = 16)	8.1 ± 4.7	8.6 ± 5.2	0.4 ± 4.9
Group B (ethinyl estradiol–norgestimate plus placebo; n = 18)	5.6 ± 3.4	5.8 ± 4.7	0.2 ± 3.7

*Levels of FSH and LH were obtained on the days of pharmacokinetic profiling in cycles 2 and 3.

gia, pain, dysmenorrhea, and anorexia. Adverse events that were considered to be related to study medication in at least 15% of subjects in group B included headache and asthenia.

Between treatment groups, a statistically significant difference was noted in the mean change from baseline for alkaline phosphatase, with a greater increase in the mean value in subjects receiving modafinil relative to the mean increase observed in subjects receiving placebo. However, there were no reports of clinically significant abnormal alkaline phosphatase levels for any subject in the study. Furthermore, at the final assessment, there were no clinically significant abnormal values reported for any laboratory test in any of the study subjects.

One of 20 subjects (5%) in group A had an episode of low diastolic blood pressure, and 4 of 21 subjects (19%) in group B had 1 or more episodes of low diastolic blood pressure, low systolic blood pressure, or both. The low diastolic blood pressures ranged from 44 mm Hg to 50 mm Hg; the low systolic blood pressure was 90 mm Hg. No clinically significant trends on vital signs were observed during the study.

DISCUSSION

Modafinil has previously been shown to induce the activity of multiple CYP enzymes, including CYP3A4/5, in primary cultures of human hepatocytes.[8] This study examined the effects of prolonged treatment with modafinil on the pharmacokinetics of 2 substrates of CYP3A4/5, ethinyl estradiol and triazolam, in healthy female volunteers. The results of the study indicated that repeated once-daily treatment with 400 mg modafinil had significant effects on the pharmacokinetics of both compounds. However, the effects of modafinil differed in type and magnitude between ethinyl estradiol and triazolam. For ethinyl estradiol, the AUC(0-τ) and C_{max} decreased only slightly (18% and 11%, respectively), with no significant change in elimination rate. For triazolam, the decreases in both AUC(0-∞) and C_{max} were large (59% and 42%, respectively), with an approximate 50% increase in the elimination rate. The safety profiles for subjects taking ethinyl estradiol–norgestimate in combination with modafinil and subjects taking ethinyl estradiol–norgestimate in combination with placebo were similar, and concomitant administration of ethinyl estradiol–norgestimate and modafinil was well tolerated.

The results of this study show that administration of modafinil for 28 days induces CYP3A4/5 activity. CYP3A4/5 are the most prevalent CYP enzymes in the liver and are the predominant CYP enzymes in the gastrointestinal tract.[21,22] Triazolam undergoes both gastrointestinal and hepatic CYP3A4/5-mediated first-pass metabolism[16]; ethinyl estradiol is subject to a smaller first-pass effect, which is only partly mediated by CYP3A4/5.[10] Therefore an induction of only intestinal CYP3A4/5 would be predicted to decrease the C_{max} for both compounds, with a larger effect on triazolam, but to have little, if any, effect on their half-lives. In contrast, induction of hepatic CYP3A4/5 would be predicted to decrease the C_{max} for both compounds and to shorten their half-lives. The results for triazolam in this study suggest that the induction is hepatic or hepatic plus intestinal. However, the lack of change in the half-life of ethinyl estradiol suggests that the intestinal component is larger than the hepatic component.

The results of a previous interaction study of modafinil and racemic warfarin support the latter conclusion.[23] Prolonged treatment with 400-mg doses of modafinil once daily had no significant effect on the single-dose pharmacokinetics of *(R)*-warfarin. *(R)*-Warfarin undergoes minimal gastrointestinal or hepatic first-pass metabolism but is eliminated primarily through metabolism by hepatic CYP3A4/5 and CYP1A2, with a possible contribution from CYP2C19.[24] The absence of any significant effect of modafinil treatment on the AUC(0-∞) or elimination rate for *(R)*-warfarin is consistent with a minimal induction of hepatic CYP3A4/5

Table VI. Number of subjects who had adverse events with an incidence of ≥15% in any treatment group

Adverse event	*Group A (ethinyl estradiol–norgestimate; n = 20)*	*Group B (ethinyl estradiol–norgestimate; n = 21)*
*Ethinyl estradiol–norgestimate treatment period**		
Headache	14 (70%)	11 (52%)
Asthenia	8 (40%)	9 (43%)
Dizziness	6 (30%)	6 (29%)
Nausea	6 (30%)	4 (19%)
Dysmenorrhea	5 (25%)	2 (10%)
Pharyngitis	4 (20%)	1 (5%)
Rhinitis	1 (5%)	5 (24%)
	Group A (ethinyl estradiol–norgestimate plus modafinil; n = 18)†	*Group B (ethinyl estradiol–norgestimate plus placebo; n = 19)†*
Ethinyl estradiol–norgestimate plus modafinil/placebo treatment period‡		
Headache	13 (72%)	10 (53%)
Asthenia	9 (50%)	11 (58%)
Nausea	6 (33%)	2 (11%)
Dizziness	5 (28%)	2 (11%)
Metrorrhagia	4 (22%)	1 (5%)
Pain	3 (17%)	1 (5%)
Dysmenorrhea	3 (17%)	1 (5%)
Anorexia	3 (17%)	0

*Treatment period beginning with the first day of cycle 1 and ending with the first administration of modafinil or placebo on day 6, 7, or 8 of cycle 2.
†Subjects who received at least 1 dose of modafinil or placebo.
‡Treatment period beginning with the first administration of modafinil or placebo on day 6, 7, or 8 of cycle 2 and continuing until the end of the study.

or CYP1A2 (which was also induced in the in vitro experiments in human hepatocytes).

Pharmacodynamic effects also were addressed in this study by measurements of plasma levels of FSH and LH during treatment with steroidal contraceptives. Between treatment groups, no statistically significant differences in the mean changes in plasma levels of either hormone were shown before or after treatment with modafinil. However, the number of subjects in the study was small, and it should be noted that because blood sampling days were selected to maximize the likelihood of detecting changes in the pharmacokinetic parameters of ethinyl estradiol, these sampling times were not optimal for detecting changes in levels of FSH or LH. The lack of a statistically significant effect on FSH and LH levels in this study should not be interpreted to mean that clinically significant pharmacodynamic effects could or would not occur in individual subjects, especially as related to the efficacy of oral contraceptives.

In conclusion, prolonged treatment of volunteer subjects with 400-mg doses of modafinil once daily caused a pronounced induction of CYP3A4/5 metabolic activity; however, the inductive effect appeared to occur largely in the gastrointestinal tract. A weaker induction of hepatic CYP3A4/5 is suggested on the basis of these results, but hepatic induction does not appear to be the major factor in the increased metabolism of ethinyl estradiol or triazolam. There is therefore potential for metabolic drug-drug interactions between modafinil and CYP3A4/5 substrates; however, clinically significant interactions would be most probable with compounds that undergo significant intestinal CYP-mediated first-pass metabolism (eg, cyclosporine [INN, ciclosporin], verapamil, lovastatin, buspirone, and triazolam). More specifically, the results of this study suggest that the efficacy of triazolam[25] could be markedly decreased during long-term treatment with 400 mg/day modafinil. They also suggest that the effectiveness of steroidal contraceptives[26-28] may be reduced when taken in combination with modafinil, and it may be expected that this effect could continue for several weeks after discontinuation of modafinil treatment. Alternative or concomitant methods of contraception are therefore recommended for women of childbearing age who are taking oral contraceptives in combination with modafinil, and it is further recommended that these alternative or concomitant methods should continue to be used for at least 1 month after discontinuation of modafinil treatment.

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References

1. Arnulf I, Homeyer P, Garma L, Whitelaw WA, Derenne JP. Modafinil in obstructive sleep apnea-hypopnea syndrome: a pilot study in 6 patients. Respiration 1997; 64:159-61.
2. Hughes RJ, Van Dongen H, Dinges DF, Rogers N, Wright KP Jr, Edgar DF, et al. Modafinil improves alertness and performance during simulated night work [abstract]. Sleep 2001;24:A200.
3. Mitler MM, Harsh J, Hirshkowitz M, Guilleminault C. Long-term efficacy and safety of modafinil (Provigil) for the treatment of excessive daytime sleepiness associated with narcolepsy. Sleep Med 2000;1:231-43.
4. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol 1998; 43:88-97.
5. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. Neurology 2000;54:1166-75.
6. Wong YN, Simcoe D, Hartman LN, Laughton WB, King SP, McCormick GC, et al. A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. J Clin Pharmacol 1999;39:30-40.
7. Moachon G, Kanmacher I, Clenet M, Matinier D. Pharmacokinetic profile of modafinil. Drugs Today 1996; 32:327-37.
8. Robertson P, DeCory HH, Madan A, Parkinson A. In vitro inhibition and induction of human hepatic cytochrome P450 enzymes by modafinil. Drug Metab Dispos 2000; 28:664-71.
9. Guengerich FP. Cytochrome P-450 3A4: regulation and role in drug metabolism. Annu Rev Pharmacol Toxicol 1999;39:1-17.
10. Guengerich FP. Metabolism of 17 alpha-ethynylestradiol in humans. Life Sci 1990;47:1981-8.
11. Orme M, Back DJ. Oral contraceptive steroids: pharmacological issues of interest to the prescribing physician. Adv Contracept 1991;7:325-31.
12. Back DJ, Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet 1990;18: 472-84.
13. Back DJ, Breckenridge AM, Crawford FE, MacIver M, Orme ML, Rowe PH. Interindividual variation and drug interactions with hormonal steroid contraceptives. Drugs 1981;21:46-61.
14. Jung-Hoffmann C, Kuhl H. Interaction with the pharmacokinetics of ethinylestradiol and progestogens contained in oral contraceptives. Contraception 1989;40:299-312.
15. Greenblatt DJ, Wright CE, von Moltke LL, Harmatz JS, Ehrenberg BL, Harrel LM, et al. Ketoconazole inhibition of triazolam and alprazolam clearance: differential kinetic and dynamic consequences. Clin Pharmacol Ther 1998;64:237-47.
16. Kroboth PD, McAuley JW, Kroboth FJ, Bertz RJ, Smith RB. Triazolam pharmacokinetics after intravenous, oral, and sublingual administration. J Clin Psychopharmacol 1995;15:259-62.
17. von Moltke LL, Greenblatt DJ, Harmatz JS, Duan SX, Harrel LM, Cotreau-Bibbo MM, et al. Triazolam biotransformation by human liver microsomes in vitro: effects of metabolic inhibitors and clinical confirmation of a predicted interaction with ketoconazole. J Pharmacol Exp Ther 1996;276:370-9.
18. Madden S, Back DJ. Metabolism of norgestimate by human gastrointestinal mucosa and liver microsomes in vitro. J Steroid Biochem Mol Biol 1991;38:497-503.
19. McGuire JL, Phillips A, Hahn DW, Tolman EL, Flor S, Kafrissen ME. Pharmacologic and pharmacokinetic characteristics of norgestimate and its metabolites. Am J Obstet Gynecol 1990;163:2127-31.
20. Gibaldi M, Perrier D. Noncompartmental analysis based on statistical moment theory. In: Pharmacokinetics. 2nd ed. New York: Marcel Dekker; 1982. p. 409-17.
21. Shen DD, Kunze KL, Thummel KE. Enzyme-catalyzed processes of first-pass hepatic and intestinal drug extraction. Adv Drug Deliv Rev 1997;27:99-127.
22. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Cytochrome P450 3A: ontogeny and drug disposition. Clin Pharmacokinet 1999;37:485-505.
23. Robertson P Jr, Hellriegel ET, Arora S, Nelson M. Effect of modafinil at steady state on the single-dose pharmacokinetic profile of warfarin in healthy volunteers. J Clin Pharmacol. In press 2002;42.
24. Kaminsky LS, Zhang ZY. Human P450 metabolism of warfarin. Pharmacol Ther 1997;73:67-74.
25. Yuan R, Flockhart DA, Balian JD. Pharmacokinetic and pharmacodynamic consequences of metabolism-based drug interactions with alprazolam, midazolam, and triazolam. J Clin Pharmacol 1999;39:1109-25.
26. Shenfield GM. Oral contraceptives. Are drug interactions of clinical significance? Drug Saf 1993;9:21-37.
27. Barditch-Crovo P, Trapnell CB, Ette E, Zacur HA, Coresh J, Rocco LE, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. Clin Pharmacol Ther 1999;65:428-38.
28. Fattore C, Cipolla G, Gatti G, Limido GL, Sturm Y, Bernasconi C, et al. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. Epilepsia 1999;40:783-7.