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PHARMACOKINETICS AND DRUG DISPOSITION

Ketoconazole inhibition of triazolam and alprazolam clearance: Differential kinetic and dynamic consequences

Background: **Kinetic and dynamic consequences of metabolic inhibition were evaluated in a study of the interaction of ketoconazole, a P4503A inhibitor, with alprazolam and triazolam, two 3A substrate drugs with different kinetic profiles.**

Methods: **In a double-blind, 5-way crossover study, healthy volunteers received (A) ketoconazole placebo plus 1.0 mg alprazolam orally, (B) 200 mg ketoconazole twice a day plus 1.0 mg alprazolam, (C)ketoconazole placebo plus 0.25 mg triazolam orally, (D) 200 mg ketoconazole twice a day plus 0.25 mg triazolam, and (E) 200 mg ketoconazole twice a day plus benzodiazepine placebo. Plasma concentrations and pharmacodynamic parameters were measured after each dose.**

Results: **For trial B versus trial A, alprazolam clearance was reduced (27 versus 86 mL/min; $P < .002$) and apparent elimination half-life ($t_{1/2}$) prolonged (59 versus 15 hours; $P < .03$), whereas peak plasma concentration (C_{max}) was only slightly increased (16.1 versus 14.7 ng/mL). The 8-hour pharmacodynamic effect areas for electroencephalographic (EEG) beta activity were increased by a factor of 1.35, and those for**

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digit-symbol substitution test (DSST) decrement were increased by 2.29 for trial B versus trial A. For trial D versus trial C, triazolam clearance was reduced (40 versus 444 mL/min; $P < .002$), $t_{1/2}$ was prolonged (18.3 versus 3.0 hours; $P < .01$), and C_{max} was increased (2.6 versus 5.4 ng/mL; $P < .001$). The 8-hour effect area for EEG was increased by a factor of 2.51, and that for DSST decrement was increased by 4.33. Observed in vivo clearance decrements due to ketoconazole were consistent with those anticipated on the basis of an in vitro model, together with in vivo plasma concentrations of ketoconazole.

Conclusion: **For triazolam, an intermediate-extraction compound, impaired clearance by ketoconazole has more profound clinical consequences than those for alprazolam, a low extraction compound. (Clin Pharmacol Ther 1998;64:237-47.)**

The triazolobenzodiazepines triazolam and alprazolam are extensively prescribed in clinical practice as hypnotic and anxiolytic-antipanic agents, respectively. Both drugs are biotransformed to parallel hydroxylated metabolites at the α- and 4-positions on the molecule.[1-4] These reactions are mediated mainly, if not entirely. by cytochrome P4503A isoforms.[1-5] However, the human pharmacokinetics of the two compounds differ substantially. Triazolam has a hepatic clearance in the "intermediate" range relative to hepatic blood flow and an elimination half-life ($t_{1/2}$) in the range of 1½ to 5 hours.[6,7] Absolute bioavailability after oral administration is approximately 50%, probably due in large part to presystemic extraction, with the likelihood of an important contribution by gastrointestinal P4503A isoforms.[7,8] In contrast, alprazolam has a hepatic clearance of less than 10% of hepatic blood flow, an elimination $t_{1/2}$ in the range of 10 to 20 hours, and absolute bioavailability generally exceeding 90%.[1,9,10]

The antifungal agent ketoconazole has been established as a highly potent inhibitor of human cytochrome P4503A isoforms, leading to large and clinically important drug interactions with a number of 3A substrate drugs, including triazolam.[3,11] Physiologically based pharmacokinetic theory predicts that the character and clinical importance of an interaction of a metabolic inhibitor such as ketoconazole with an orally administered substrate drug will depend on the hepatic clearance and presystemic extraction of this substrate.[12-16] We evaluated the magnitude and clinical consequences of the interaction of ketoconazole with triazolam and alprazolam, and the extent to which these in vivo interactions are consistent with in vitro interactions observed in human liver microsomes.

METHODS

Design. The protocol was reviewed and approved by the Human Investigation Review Committee serving Tufts University School of Medicine and New England Medical Center Hospital. Seven healthy male volunteers (age range, 21 to 44 years) participated after each gave written informed consent. All were active ambulatory nonsmoking adults, with no evidence of medical disease and taking no other medications.

The study had a double-blind, single-dose, 5-way crossover design. Medications were packaged identically in opaque capsules and administered orally, with at least 7 days elapsing between trials (Table I). The 5 treatment conditions were as follows:

A. Ketoconazole placebo plus 1.0 mg alprazolam
B. Ketoconazole (200 mg) plus 1.0 mg alprazolam
C. Ketoconazole placebo plus 0.25 mg triazolam
D. Ketoconazole (200 mg) plus 0.25 mg triazolam
E. Ketoconazole (200 mg) plus benzodiazepine placebo

Procedures. At 8 AM on study day 1, subjects entered the outpatient Psychopharmacology Research Unit, where they received 200 mg ketoconazole (or placebo) and underwent practice trials with the rating instruments and psychomotor testing procedures described below. Subjects took a second dose of ketoconazole (or placebo) at home on the evening of day 1, and the third dose in the outpatient unit the morning of day 2. In the evening of day 2 they were admitted to the General Clinical Research Center at New England Medical Center Hospital where they received their fourth dose of ketoconazole or placebo. They remained in the General Clinical Research Center for the next 36 hours.

Subjects ingested a standardized light breakfast, with no caffeine-containing beverages, at approximately 7:30 AM on the morning of day 3. They continued to fast until 12 noon, after which they resumed a normal diet (without caffeine-containing beverages). The fifth dose of ketoconazole (or placebo) was given at 8 AM, and the single challenge dose of triazolam, alprazolam, or placebo was given at 9 AM.

Venous blood samples were drawn from an indwelling cannula into heparinized tubes before administration and at the following times after administration: ½, 1, 1½, 2, 3, 4, 6, 8, and 12 hours. Two additional samples were drawn at 24 and 48 hours. Samples were centrifuged, and the plasma was separated and frozen until the time of assay.

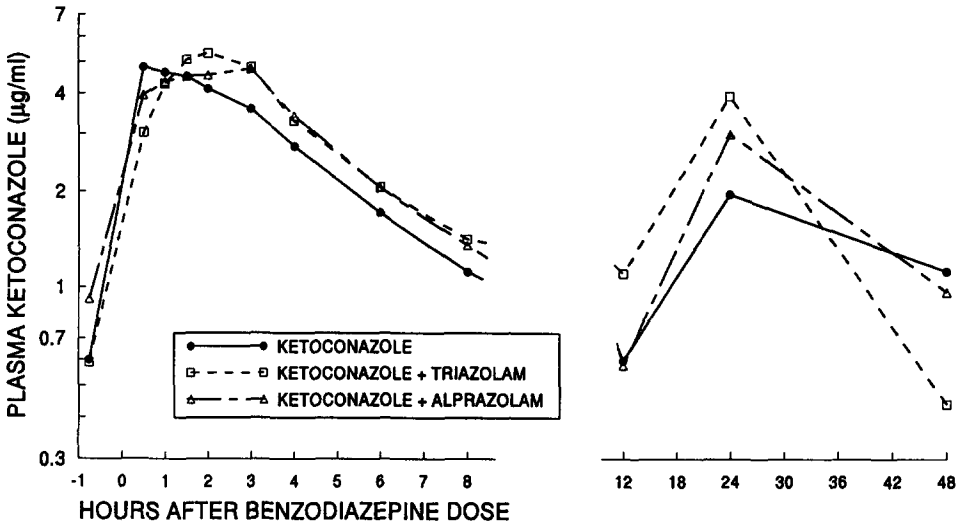

Figure 1. Mean plasma ketoconazole concentrations when ketoconazole was administered alone (trial E), with triazolam (trial D), or with alprazolam (trial B).

Table I. Summary of study design

	Day 1		*Day 2*		*Day 3*			*Day 4*	
Trial	*AM*	*PM*	*AM*	*PM*	*8 AM*	*9 AM*	*PM*	*AM*	*PM*
A	P	P	P	P	P	ALP	P	P	P
B	K	K	K	K	K	ALP	K	K	K
C	P	P	P	P	P	TRZ	P	P	P
D	K	K	K	K	K	TRZ	K	K	K
E	K	K	K	K	K	P	K	K	K

P, Placebo; K, 200 mg ketoconazole; ALP, 1.0 mg alprazolam; TRZ, 0.25 mg triazolam.

Table II. Pharmacokinetic interaction of ketoconazole with triazolam and alprazolam

	*Control**	*With ketoconazole**	*Values of Student t test*
Triazolam study (n = 6)			
C_{max} (ng/mL)	2.6 ± 0.3	5.4 ± 0.4	7.28 ($P < .001$)
t_{max} (h after dose)	1.2 ± 0.2	1.9 ± 0.4	1.96 (NS)
Elimination $t_{½}$ (h)	3.0 ± 0.3	18.3 ± 4.0	4.14 ($P < .01$)
Total AUC (ng/mL · h)	10.6 ± 1.6	145.4 ± 39.1	3.58 ($P < .02$)
Oral CL (mL/min)	444 ± 73	39.6 ± 10.5	6.44 ($P < .002$)
Alprazolam study (n = 7)			
C_{max} (ng/mL)	14.7 ± 1.6	16.1 ± 1.4	1.16 (NS)
t_{max} (h after dose)	1.4 ± 0.3	1.5 ± 0.2	0.40 (NS)
Elimination $t_{½}$ (h)	15.2 ± 2.1	59 ± 17	2.85 ($P < .03$)
Total AUC (ng/mL · h)	237 ± 43	944 ± 277	2.85 ($P < .03$)
Oral CL (mL/min)	86 ± 16	27 ± 7	5.49 ($P < .002$)

C_{max}, Peak plasma concentration; t_{max}, time to reach C_{max}; $t_{½}$, half-life; AUC, area under the plasma concentration versus time curve; CL, clearance.
*Mean ± SE values.

An 8-electrode electroencephalographic (EEG) montage was affixed as follows: left and right frontal (F3, F4), left and right central (C3, C4), as well as midline frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz), with a nose electrode as reference. Procedures for preparation of electrode sites and affixing of electrodes have been

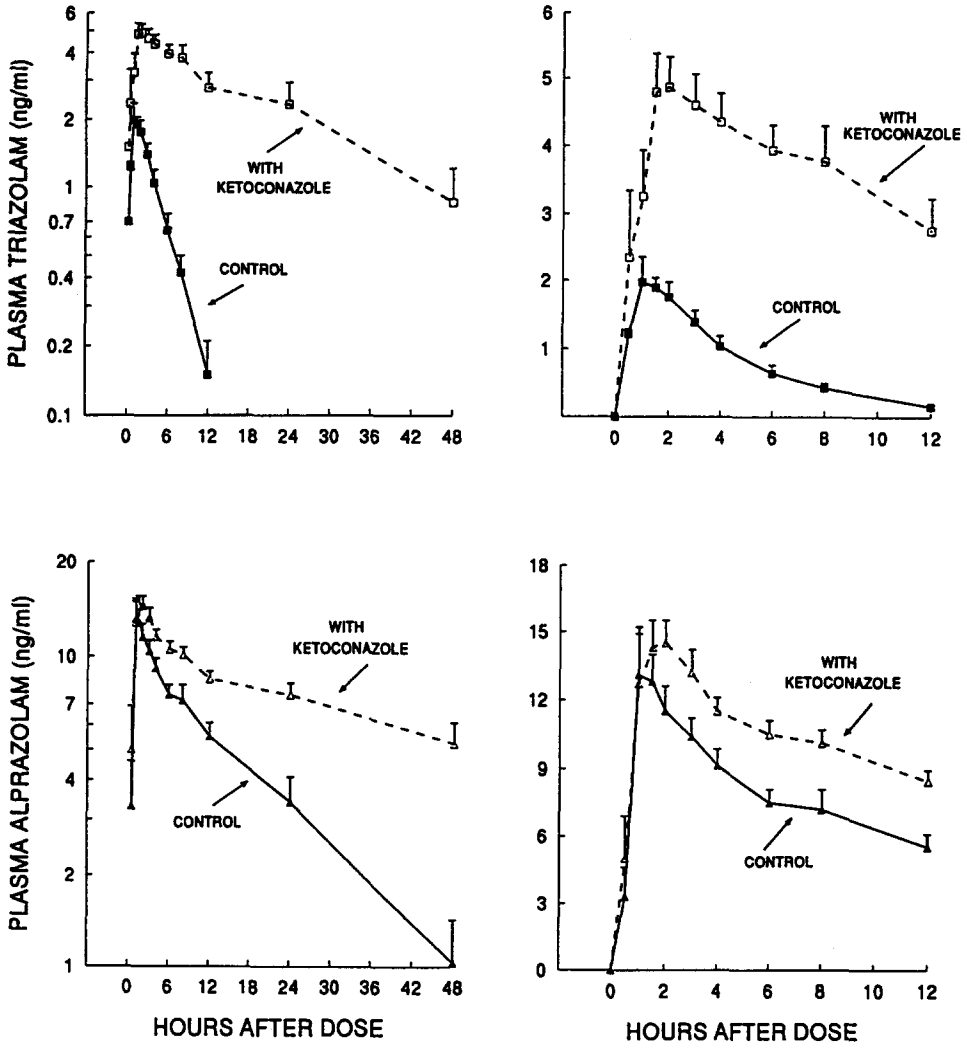

Figure 2. Upper left panel, Mean ± SE plasma triazolam concentrations after 0.25 mg triazolam alone (trial C, control) and with coadministration of ketoconazole (trial D), shown with a logarithmic concentration axis. **Upper right panel,** The first 8 hours after administration, shown with a linear concentration axis. **Lower left panel,** Mean ± SE plasma alprazolam concentrations after 1.0 mg alprazolam alone (trial A, control) and with coadministration of ketoconazole (trial B), shown with a logarithmic concentration axis. **Lower right panel,** The first 8 hours after administration, shown with a linear concentration axis.

described previously.[3,17-20] The EEG was recorded in 4-second epochs for as long as necessary to ensure at least 2 minutes of artifact-free information, before administration, and at times corresponding to blood samples up to 24 hours after administration. Data were digitized over the power spectrum from 4 to 30 cycles per second (Hz), and analyzed by fast Fourier transform to determine amplitude in the total spectrum (4 to 30 Hz) and in the beta (12 to 30 Hz) frequency range.

Subjects' self-ratings of sedative effects and mood state were obtained on a series of 100-mm visual analog scales.[3,17,20,21] Ratings of sedation were also performed by a trained observer, using the same rating instrument, without knowledge of the treatment condition. Self- and observer-ratings were obtained twice before medication administration and at ½, 1, 1½, 2, 3, 4, 6, and 8 after administration.

The digit symbol substitution test (DSST) was administered twice before dosing and at times corresponding to rating scales.[3,17,20,21] Subjects were asked to make as many correct symbol-for-digit substitutions as possible within a 2-minute period. Subjects com-

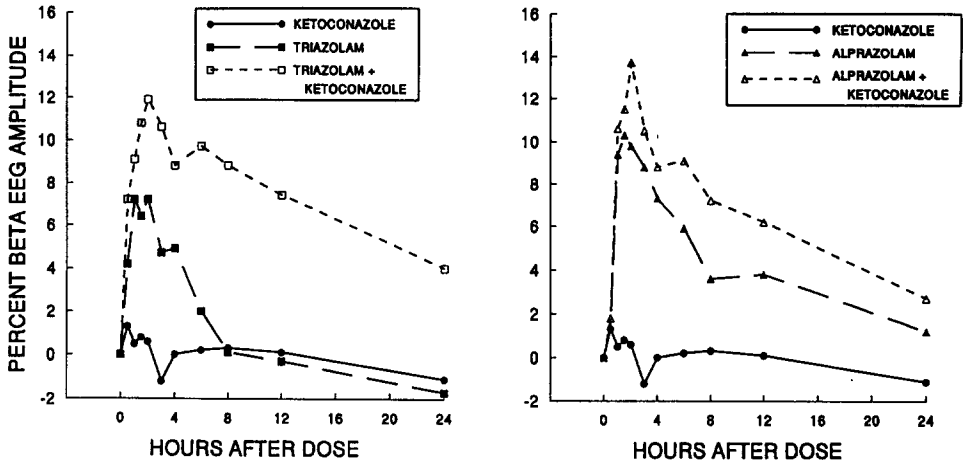

Figure 3. Changes over predose baseline in percentage of electroencephalographic (EEG) amplitude falling in the beta frequency range; values are the mean of left and right frontal leads. Each *point* is the mean for all subjects at the corresponding time. Standard errors for individual data points, omitted for clarity, are available from the authors on request. **Left panel,** Results with triazolam alone (trial C), triazolam plus ketoconazole (trial D), and ketoconazole alone (trial E). **Right panel,** Results with alprazolam alone (trial A), alprazolam plus ketoconazole (trial B), and ketoconazole alone (trial E).

Table III. AUC of EEG change versus time, based on mean values of percent beta amplitude from left and right frontal leads

	AUC(0-8)	*AUC(0-12)*	*AUC(0-24)*
Triazolam study (n = 6)			
Trial C (triazolam)*	29.7 ± 8.7	27.5 ± 10.9	15.8 ± 12.1
Trial D (triazolam and ketoconazole)*	74.5(±10.1)	106.9 ± 9.8	174.9 ± 14.6
Trial E (ketoconazole)*	1.4 ± 4.4	1.0 ± 8.0	–8.0 ± 13.2
Value of F	18.1 ($P < .001$)†	48.1 ($P < .001$)†	52.51 ($P < .001$)‡
Alprazolam study (n = 7)			
Trial A (alprazolam)*	53.0 ± 12.3	67.8 ± 12.1	97.9 ± 19.4
Trial B (alprazolam and ketoconazole)*	71.3 ± 11.1	98.1 ± 11.7	151.0 ± 11.0
Trial E (ketoconazole)*	1.2 ± 3.7	1.9 ± 6.9	–4.3 ± 11.7
Value of F	21.4 ($P < .001$)§	32.1 ($P < .001$)†	30.5 ($P < .001$)†

EEG, Electroencephalographic; AUC(0-8), AUC from 0 to 8 hours; AUC(0-12), AUC from 0 to 12 hours; AUC(0-24), AUC from 0 to 24 hours.
*Mean ± SE AUC values.
†Each trial significantly different ($P < .05$) from the other (Student-Newman-Keuls comparison).
‡Trial D significantly different from C and E; C and E not significantly different (Student-Newman-Keuls comparison).
§Trials A and B significantly different from E; A and B not significantly different (Student-Newman-Keuls comparison).

pleted equivalent DSST variants, with no individual taking the same test more than once.

Acquisition and recall of information were evaluated using a word-list free recall procedure that was administered 1½ hours after benzodiazepine or placebo administration.[3,17,21,22] Sixteen words, taken from 4 different categories, were read in random order in "shopping-list" fashion. Recall was tested immediately after presentation of the list, as subjects wrote list items in any order. The list was then presented in a different random order, with subjects again writing down the items immediately. This was repeated a total of 6 times. At 24 hours after dosing, subjects were asked to remember as many words as possible from the list (free recall); thereafter, the same list was read in 6 different random sequences.

Analysis of data. Plasma concentrations of triazolam and alprazolam were determined by gas chromatography with electron-capture detection.[3,6,23,24] Plasma concentrations of ketoconazole were determined by HPLC.[3]

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