Comparative Kinetics and Response to the Benzodiazepine Agonists Triazolam and Zolpidem: Evaluation of Sex-Dependent Differences

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ABSTRACT

Eighteen healthy volunteers (10 men and 8 women) participated in a single-dose, double-blind, three-way crossover pharmacokinetic and pharmacodynamic study. Treatment conditions were 0.25 mg of triazolam, a full-agonist benzodiazepine ligand; 10 mg of zolpidem, an imidazopyridine having relative selectivity for the type 1 benzodiazepine receptor subtype; and placebo. Weight-normalized clearance of triazolam was higher in women than in men (8.7 versus 5.5 ml/min/kg), but the difference was not significant. In contrast, zolpidem clearance was lower in women than in men (3.5 versus 6.7 ml/min/kg, \( P < .06 \)). Compared to placebo, both active medications produced significant benzodiazepine agonist-like pharmacodynamic effects: sedation, impaired psychomotor performance, impaired information recall, and increased electroencephalographic \( \beta \)-amplitude. Effects of triazolam and zolpidem in general were comparable and less than 8 h in duration. There was no evidence of a substantial or consistent sex difference in pharmacodynamic effects or in the kinetic-dynamic relationship, although subtle differences could not be ruled out due to low statistical power. The complete dependence of triazolam clearance on CYP3A activity, as opposed to the mixed CYP participation in zolpidem clearance, may explain the differing sex effects on clearance of the two compounds.

The influence of sex (gender) on the pharmacokinetics and pharmacodynamics of psychotropic drugs is an issue of current scientific and clinical concern. A number of recent reviews have considered whether the expression and/or activity of various CYP enzymes may differ between men and women, thereby leading to differences in pharmacokinetics that are not explained by sex-dependent differences in body weight (Dawkins and Potter, 1991; Yonkers et al., 1992; Harris et al., 1995; Pollock, 1997). Much of the focus research on the CYP3A isoforms, known to be partially or entirely responsible for the biotransformation of many psychotropic drugs (von Moltke et al., 1995; Thummel and Wilkinson, 1998). Some studies suggest that CYP3A activity may be higher in women than in men, leading to higher clearances of some CYP3A substrates in women (Greenblatt et al., 1994; Gorski et al., 1998; Schroeder et al., 1998). The differences may be more evident for orally administered CYP3A substrates that ordinarily undergo extensive presystemic extraction, with a significant apparent contribution of CYP3A isoforms located in gastrointestinal tract mucosal cells. However, the experimental data on this topic are not consistent, and there is much conflicting evidence. Also of concern are possible sex-dependent differences in intrinsic drug sensitivity, although data on this topic are sparse.

Anxiolytic and hypnotic medications that are benzodiazepine receptor agonists continue to be extensively prescribed in clinical practice for the treatment of anxiety, panic disorder, and sleep disorders. Until the early 1990s, essentially all such medications had a benzodiazepine structure and were full-agonist \( \gamma \)-aminobutyric acid-benzodiazepine receptor ligands (Hollister et al., 1993; Shader and Greenblatt, 1993). The imidazopyridine derivative zolpidem was introduced into clinical practice as a hypnotic agent a number of years ago and is widely used throughout the world (Langtry and Benfield, 1990; Hoehns and Perry, 1993; Undén and Roth-Schechter, 1996; Darcourt et al., 1999). Although not a benzodiazepine in structure, zolpidem is a \( \gamma \)-aminobutyric acid-
benzodiazepine receptor agonist with relative selectivity for the type 1 benzodiazepine receptor subtype (Sanger et al., 1994). The clinical importance of this neuropharmacological property is controversial (Lobo and Greene, 1997; Rush, 1998). Most clinical studies comparing the pharmacodynamic properties of zolpidem with those of a typical nonselective full-agonist benzodiazepine such as triazolam do not detect consistent pharmacodynamic differences after comparably potent single doses (Berlin et al., 1993; Rush and Griffiths, 1996; Mattila et al., 1998; Rush et al., 1998; Mintzer and Griffiths, 1999). Nor are there consistent differences between zolpidem and triazolam in hypnotic efficacy during treatment of sleep disorders (Nowell et al., 1997). Zolpidem, like triazolam, has a short elimination half-life (Durand et al., 1992; Salvà and Costa, 1995; Greenblatt et al., 1998a) and has low likelihood of producing residual daytime sedation after nighttime administration (Undén and Roth-Schechter, 1996). Some data indicate that zolpidem has a reduced likelihood of producing discontinuation or withdrawal phenomena after treatment is stopped (Monti et al., 1994; Ware et al., 1997). Another distinguishing property of zolpidem is that its bio- transformation is only partially (about 60%) mediated by CYP3A (Pichard et al., 1995; von Moltke et al., 1999), whereas clearance of triazolam is fully dependent on CYP3A (von Moltke et al., 1996). As a consequence, coadministration of strong CYP3A inhibitors such as ketoconazole or itraconazole produces far less impairment of zolpidem clearance than of triazolam clearance (von Moltke et al., 1996; Greenblatt et al., 1998a,b).

The present study compared the kinetics and dynamics of single clinically comparable doses of triazolam and zolpidem in healthy young male and female volunteers. The objectives were to evaluate the comparative pharmacodynamics of the two compounds using a variety of subjective and objective measures of benzodiazepine agonist activity and to assess possible sex-dependent differences in the kinetics and responses to both drugs.

Materials and Methods

Subjects and Procedure. The study protocol was reviewed and approved by the Human Investigation Review Committee serving Tufts University School of Medicine and New England Medical Center. Male and female volunteers, aged 22 to 41 years, participated after giving written informed consent. All were healthy ambulatory adults, with no evidence of medical disease and receiving no other medications. Females were not taking oral contraceptives.

Subjects participated in a four-way crossover study. To allow volunteers to adapt to the study setting and procedures and to minimize the effects of practice, the first treatment in the sequence was a single-blind administration of placebo; data from this practice trial were not used in subsequent analyses. The next three treatments were double-blind and randomized in sequence. The three conditions were placebo, 0.25 mg triazolam, and 10 mg zolpidem. At least 7 days elapsed between treatments. All medications were identical packaged.

On the morning of each study day, after ingesting a standardized light breakfast with no caffeine-containing food or beverages and no grapefruit juice, subjects arrived at the Research Unit at approximately 7:30 AM. They fasted until 12:00 noon, after which they resumed a normal diet (without grapefruit juice or caffeine-containing food or beverages). The single dose of the study medication was given with 240 ml of tap water at 8:00 AM.

Venous blood samples were drawn from an indwelling cannula into heparinized tubes prior to dosing and at the following postdosing times: 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, and 24 h. Samples were centrifuged, and the plasma was separated and frozen until the time of assay.

The electroencephalogram (EEG) was recorded using a six-electrode montage, with instrumentation and methodology described previously (Greenblatt et al., 1994, 1998a,b; von Moltke et al., 1996). At two predosing times and during 8 h postdosing at times corresponding to blood sampling, the EEG was quantified in 4-s epochs for as long as necessary to ensure at least 2 min of artifact-free recording. Data were digitized over the power spectrum from 4.0 to 31.75 cycles/s (Hz) and then fast Fourier-transformed to determine amplitude over the 4.0- to 31.75-Hz spectrum and in the beta (13.0–31.75 Hz) band.

Subjects’ self-ratings of sedative effects and mood state were obtained using a series of 100-mm visual-analog scales (Scavone et al., 1998). Ratings of sedation were also performed by trained observers, using the same rating instrument, without knowledge of the treatment condition. Self- and observer ratings were obtained twice before medication administration and at postdosing times indicated earlier.

The digit symbol substitution test (DSST) was administered twice prior to dosing and at times corresponding to rating scales (Greenblatt et al., 1991, 1994, 1998a,b; von Moltke et al., 1996). Subjects were asked to make as many correct symbol-for-digit substitutions as possible within a 2-min period. Subjects completed 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 at 1.5 h after drug or placebo administration (Greenblatt et al., 1991, 1994, 1998a,b; von Moltke et al., 1996). Sixteen words, taken from four different categories, were read in random order in “shopping-list” fashion. Subjects wrote down items immediately after lists were presented in random order. List presentation and recall were repeated a total of six times at 1.5 h after dosing. At 24 h after dosing, subjects were asked to remember as many words as possible from the previous day’s list (delayed or “free” recall). Thereafter, the same lists were read in the same sequence in which they were presented on the previous day to assess whether residual effects of drug administration on immediate recall were detectable.

Analysis of Data. Plasma concentrations of triazolam were determined by gas chromatography with electron-capture detection, having a sensitivity limit of 0.2 ng/ml for a 2-ml sample (von Moltke et al., 1996). The variance for replicate samples did not exceed 8%, and the between-day variance for a quality control sample was 4.3%. Plasma concentrations of zolpidem were determined by HPLC with fluorescence detection (Durol and Greenblatt, 1997). The sensitivity limit was 1 to 2 ng/ml, and the variance between replicate samples did not exceed 8%.

The slope (β) of the terminal log-linear phase of each triazolam or zolpidem plasma concentration-versus-time curve was determined by linear regression analysis. This slope was used to calculate the apparent elimination half-life. Area under the plasma concentration curve from time 0 until the last detectable concentration was determined by the linear trapezoidal method. To this area was added the residual area extrapolated to infinity, calculated as the final concentration divided by β, yielding the total area under the plasma concentration-versus-time curve (AUC). The peak plasma concentration and the time of peak concentration represented the rate of appearance of drug in systemic circulation. Apparent oral clearance was calculated as the administered dose divided by the total AUC. Since triazolam or zolpidem was not detectable in the 24-h plasma samples, calculation of pharmacokinetic parameters was based on an 8-h duration of sampling. For some subjects, the duration of sampling during the terminal phase did not exceed three times the estimated half-life. This is a potential weakness in the pharmacokinetic methodology.

For self- and observer ratings on visual-analog scales, the two
predosing baseline ratings were averaged, and postdosing scores were expressed as the increment or decrement relative to the mean predosing value. Scores on the DSST were analyzed similarly. The word-list memory test was analyzed as the mean absolute number of words correctly remembered for delayed recall and as mean number of words remembered after six trials for immediate recall.

For each EEG recording session, the relative β-amplitudes (β divided by total, expressed as percent) were calculated, and values from the left and right frontotemporal leads were averaged. The means of the relative β-amplitudes in the predosing recordings were used as baseline, and all postdosing values were expressed as the increment or decrement over that treatment’s mean predosing baseline value.

For each pharmacodynamic variable, the area under the 4-h plot of effect change score versus time was calculated to obtain a single integrated measure of pharmacodynamic action during the period of greatest drug effect. The ratio (RAUC) of 4-h pharmacodynamic integrated measure of pharmacodynamic action during the period of effect change score versus time was calculated to obtain a single line value.

TABLE 1
Subject characteristics and kinetic variables for triazolam and zolpidem

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 10)</th>
<th>Women (n = 8)</th>
<th>Value of Student’s t (men versus women)</th>
<th>Values for All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject characteristics</td>
<td></td>
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</tr>
<tr>
<td>Age (yr)</td>
<td>26 ± 4.1 (20–33)</td>
<td>28 ± 5.6 (22–48)</td>
<td>1.22 (P &gt; 0.2) (20–38)</td>
<td>27 ± 4.9 (23–33)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.3 ± 10.5 (63–94)</td>
<td>66.8 ± 8.7 (58–84)</td>
<td>1.85 (P &lt; .1) (71.5 ± 10.4)</td>
<td>175 ± 9.4 (82–105)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180 ± 6 (169–189)</td>
<td>168 ± 9 (152–178)</td>
<td>3.38 (P &lt; .005) (152–189)</td>
<td></td>
</tr>
<tr>
<td>Kinetic variables for triazolam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>3.0 ± 1.3 (1.6–6.3)</td>
<td>2.3 ± 1.2 (1.2–5.4)</td>
<td>1.06 (P &gt; .3) (1.2–6.3)</td>
<td>2.7 ± 1.4 (1.1–4.4)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>1.25 ± 0.9 (0.5–3.0)</td>
<td>1.25 ± 0.6 (0.5–2.0)</td>
<td>0 (0.5–3.0)</td>
<td>1.25 ± 0.7 (0.5–3.0)</td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>2.71 ± 0.4 (2.3–3.5)</td>
<td>2.74 ± 1.0 (1.5–4.4)</td>
<td>0.08 (P &lt; .005) (1.5–4.4)</td>
<td>2.72 ± 0.72 (1.3–4.4)</td>
</tr>
<tr>
<td>Apparent oral clearance</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ml/min</td>
<td>407 ± 136 (246–725)</td>
<td>568 ± 382 (177–1210)</td>
<td>1.25 (P &gt; .2) (177–1210)</td>
<td>479 ± 277 (177–1210)</td>
</tr>
<tr>
<td>ml/min/kg</td>
<td>5.5 ± 1.8 (3.2–9.0)</td>
<td>8.7 ± 6.3 (2.5–21.0)</td>
<td>1.57 (P &gt; .1) (2.5–21.0)</td>
<td>6.9 ± 4.6 (2.5–21.0)</td>
</tr>
<tr>
<td>Kinetic variables for zolpidem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>119 ± 40 (70–189)</td>
<td>140 ± 43 (96–214)</td>
<td>1.07 (P &gt; 0.2) (70–214)</td>
<td>128 ± 42 (96–214)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>1.20 ± 0.35 (1.0–2.0)</td>
<td>1.56 ± 1.18 (0.5–1.0)</td>
<td>0.93 (P &gt; 0.3) (0.5–1.0)</td>
<td>1.36 ± 0.8 (0.5–1.0)</td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>1.64 ± 0.42 (0.84–2.29)</td>
<td>2.65 ± 0.97 (1.86–4.75)</td>
<td>2.97 (P &lt; 0.01) (2.08 ± 0.86)</td>
<td></td>
</tr>
<tr>
<td>Apparent oral clearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ml/min</td>
<td>486 ± 260 (291–1127)</td>
<td>230 ± 60 (157–319)</td>
<td>2.71 (P &lt; 0.02) (373 ± 233)</td>
<td></td>
</tr>
<tr>
<td>ml/min/kg</td>
<td>6.7 ± 4.3 (3.1–17.9)</td>
<td>3.5 ± 0.9 (2.2–4.8)</td>
<td>2.10 (P &lt; 0.06) (5.3 ± 3.6)</td>
<td>2.2–17.9</td>
</tr>
</tbody>
</table>

Results

Clinical Effects. Two subjects withdrew from the study because of nausea developing at 1 to 2 h after zolpidem administration; they were replaced with two other subjects. Data analysis represents the 18 participants that completed all treatment conditions. Characteristics are shown in Table 1.

Pharmacokinetics. Triazolam attained peak plasma concentration on average at 1.25 h after dosing (Table 1, Fig. 1). The mean elimination half-life was 2.7 h, with a range of 1.8 to 3.9 h. Sex did not significantly influence elimination half-life. Oral clearance of triazolam, both with and without normalization for body weight, was higher in women than in men; however, there were large individual variations within each group, and differences were not statistically significant.

Peak plasma concentrations of zolpidem were reached on average at 1.4 h after dosing (Table 1, Fig. 1). Elimination half-life was significantly shorter in men than in women, and oral clearance (in milliliters per minute) was significantly higher (P < .02) in men. After normalization for body weight, the difference in zolpidem clearance between men and women approached significance (P < .06).

Pharmacodynamic Effects. ANOVA indicated no significant differences among the three treatments in predosing baseline values of any of the pharmacodynamic variables.
Triazolam and zolpidem both produced pharmacodynamic effects consistent with benzodiazepine receptor agonism. These effects included increased EEG amplitude in the β-frequency range, impaired performance on the DSST, and increases in self-ratings and observer ratings of sedation (Figs. 2 and 3). These effects were of relatively short duration; by 4 to 8 h after dosing, values were generally indistinguishable from those associated with placebo. Placebo itself produced no evidence of benzodiazepine agonist activity.

Analyses of areas under the 4-h pharmacodynamic effect area indicated that triazolam and zolpidem produced quantitatively comparable changes in EEG amplitude, DSST score decrements, and observer-rated sedation (Table 2). The effects of zolpidem on self-rated sedation were slightly greater than those of triazolam.

Significant differences among the three treatment conditions were also observed in mood scale items of thinking slowed, feeling “spacey”, and feeling nervous (Fig. 3, Table 2). It is of interest that self-ratings of feeling “spacey” and feel-
ing nervous were significantly greater with zolpidem than with either placebo or triazolam. Zolpidem also produced greater changes in the direction of “thinking slowed down”, although not significantly different from the other two treatments.

Each 4-h pharmacodynamic effect area for each treatment condition was then separated into mean values for men and women, respectively (Table 3, Fig. 4). For only one of the comparisons (self-rated sedation in the zolpidem treatment condition) did the male-female difference approach significance ($P < .1$); for all other comparisons, sex differences were not significant ($P > .1$).

The word-list test of information acquisition and recall indicated small decrements associated with triazolam and zolpidem, compared to placebo, in number of words remembered after six learning trials at 1.5 h after dosing (Fig. 5). Differences among the three treatments approached significance ($P < .06$). Triazolam and zolpidem both produced similar large and highly significant decrements in free recall (delayed recall) at 24 h after dosing (Fig. 5). The three treatments did not differ significantly in number of words recalled after six relearning trials at 24 h after dosing. There were no significant differences between men and women in number of words remembered in any of the treatment conditions.

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**Table 2**

Area under the curve of pharmacodynamic effect change score versus time from zero through 4 h after dosage.

*Values are given as mean ± S.D., with 95% CI in parentheses (n = 8).*

<table>
<thead>
<tr>
<th>Dynamic Variable</th>
<th>Placebo</th>
<th>Triazolam</th>
<th>Zolpidem</th>
<th>Value of F from ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG β-amplitude (frontal leads)</td>
<td>$-4.6 \pm 9.3$</td>
<td>$21.4 \pm 11.6$</td>
<td>$16.3 \pm 12.8$</td>
<td>31.7 ($P &lt; .001$)*</td>
</tr>
<tr>
<td>DSSST score</td>
<td>$8.2 \pm 17.7$</td>
<td>$-45.8 \pm 39.8$</td>
<td>$-45.4 \pm 27.7$</td>
<td>19.6 ($P &lt; .001$)*</td>
</tr>
<tr>
<td>Self-rated sedation</td>
<td>$-2.4 \pm 21.5$</td>
<td>$21.8 \pm 43.7$</td>
<td>$30.2 \pm 51.7$</td>
<td>3.24 ($P &lt; .06$)*</td>
</tr>
<tr>
<td>Observer-rated sedation</td>
<td>$-0.2 \pm 8.6$</td>
<td>$47.3 \pm 36.8$</td>
<td>$49.8 \pm 40.5$</td>
<td>18.8 ($P &lt; .001$)*</td>
</tr>
<tr>
<td>Rating scale items</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calm/anxious</td>
<td>$-4.0 \pm 33.8$</td>
<td>$-20.0 \pm 40.1$</td>
<td>$-3.2 \pm 32.0$</td>
<td>1.35 (NS)</td>
</tr>
<tr>
<td>Energetic/fatigued</td>
<td>$-4.4 \pm 25.6$</td>
<td>$-2.1 \pm 45.5$</td>
<td>$8.0 \pm 75.8$</td>
<td>0.25 (NS)</td>
</tr>
<tr>
<td>Thinking slowed down/thinking speeded up</td>
<td>$10.5 \pm 45.6$</td>
<td>$-7.9 \pm 20.8$</td>
<td>$-25.0 \pm 41.3$</td>
<td>3.47 ($P &lt; .05$)</td>
</tr>
<tr>
<td>Normal/spacy</td>
<td>$-4.9 \pm 29.2$</td>
<td>$24.9 \pm 50.2$</td>
<td>$56.6 \pm 59.8$</td>
<td>9.49 ($P &lt; .001$)*</td>
</tr>
<tr>
<td>At ease/nervous</td>
<td>$-17.7 \pm 25.4$</td>
<td>$-15.9 \pm 30.2$</td>
<td>$12.8 \pm 39.2$</td>
<td>5.84 ($P &lt; .01$)*</td>
</tr>
<tr>
<td>Relaxed/excited</td>
<td>$-5.9 \pm 27.7$</td>
<td>$-13.3 \pm 23.3$</td>
<td>$-3.1 \pm 30.8$</td>
<td>0.63 (NS)</td>
</tr>
</tbody>
</table>

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**Table 3**

Gender effects on 4-h pharmacodynamic effect areas and ratios of effect area to plasma AUC (RAUCs).

*Each value is the mean ± S.D., with 95% confidence interval in parentheses, for 10 male and 8 female subjects.*

<table>
<thead>
<tr>
<th>4-h effect areas</th>
<th>Placebo</th>
<th>Triazolam</th>
<th>Zolpidem</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG β-amplitude (frontal leads)</td>
<td>$-1.9 \pm 8.1$</td>
<td>$20.2 \pm 13.9$</td>
<td>$15.6 \pm 11.2$</td>
</tr>
<tr>
<td>DSSST score</td>
<td>$8.5 \pm 18.3$</td>
<td>$-52.7 \pm 44.5$</td>
<td>$-36.2 \pm 29.5$</td>
</tr>
<tr>
<td>Self-rated sedation</td>
<td>$-0.6 \pm 23.2$</td>
<td>$7.7 \pm 23.5$</td>
<td>$11.9 \pm 50.7$</td>
</tr>
<tr>
<td>Observer-rated sedation</td>
<td>$1.3 \pm 7.6$</td>
<td>$56.7 \pm 33.7$</td>
<td>$44.9 \pm 32.5$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAUC values (4-h effect area divided by plasma AUC)</th>
<th>Placebo</th>
<th>Triazolam</th>
<th>Zolpidem</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG β-amplitude (frontal leads)</td>
<td>$1.9 \pm 1.2$</td>
<td>$2.7 \pm 1.5$</td>
<td>$0.05 \pm 0.04$</td>
</tr>
<tr>
<td>DSSST score</td>
<td>$-5.0 \pm 4.4$</td>
<td>$-3.0 \pm 5.0$</td>
<td>$-0.12 \pm 0.14$</td>
</tr>
<tr>
<td>Self-rated sedation</td>
<td>$1.0 \pm 2.31$</td>
<td>$0.90 \pm 7.17$</td>
<td>$0.05 \pm 0.14$</td>
</tr>
<tr>
<td>Observer-rated sedation</td>
<td>$5.2 \pm 2.5**$</td>
<td>$2.5 \pm 2.2**$</td>
<td>$0.16 \pm 0.12**$</td>
</tr>
</tbody>
</table>

**Comparisons between male and female groups indicated no significant difference ($P > .1$) except as noted: * $P < .1$, ** $P < .05$.**
Kinetic-Dynamic Relationships. Evaluation of mean pharmacodynamic effect change scores versus mean plasma triazolam concentrations at corresponding times indicated evidence of counterclockwise hystereses, consistent with a delay in equilibration of triazolam between plasma and hypothetical effect site. Based on the aggregate data for all subjects, the mean value of apparent half-life of equilibration corresponding to $K_{EO}$ ($t_{1/2KEO}$) was 10.2 min when EEG $\beta$-amplitude was used as the pharmacodynamic effect variable (Fig. 6). Hypothetical effect site triazolam concentrations were significantly related to EEG effect change measures using an exponential concentration-effect link model (Laurijssens and Greenblatt, 1996). When male and female subjects were evaluated separately, $t_{1/2KEO}$ values were 8.4 and 10.0 min, respectively (Fig. 6). Corresponding $t_{1/2KEO}$ values were 11.0 min using DSST change score as the effect measure and 12.7 min using observer-rated sedation as the effect measure. When male and female subjects were evaluated separately, resulting $t_{1/2KEO}$ values were not significantly different.

Evaluation of the concentration-response relationship for zolpidem indicated no evidence of an apparent effect site equilibration delay. The relation of plasma zolpidem concentration to pharmacodynamic effect change was consistent with an exponential link model. The functional relationships were not significantly different between male and female subjects.

Comparison of RAUC values for observer-rated sedation suggested higher values (greater drug sensitivity) in men for both triazolam ($P < .05$) and zolpidem ($P < .1$) treatments (Table 3). For other pharmacodynamic variables, RAUC values were not significantly different ($P > .1$) between men and women.

Discussion

The triazolobenzodiazepine triazolam is a “pure” substrate for human CYP3A, being metabolized to its $\alpha$-hydroxy and 4-hydroxy metabolites solely by isoforms of this subfamily (von Moltke et al., 1996). Crossover studies of i.v. and oral triazolam in healthy volunteers indicate that its oral bioavailability averages 40 to 50% (Kroboth et al., 1995). This is lower than the hepatic extraction ratio calculated from clearance of i.v. triazolam together with typical values of hepatic
blood flow and indicates that gastrointestinal CYP3A is likely to contribute to net presystemic extraction of orally administered triazolam. In the present study, values of weight-normalized oral clearance of triazolam were higher in women than in men. However, the difference did not reach statistical significance due to the large individual variability within groups. We observed similar nonsignificant differences between young men and women in three previous studies of orally administered triazolam (Greenblatt et al., 1983b, 1991; Smith et al., 1983); in a fourth study, oral clearance of triazolam also was higher in women than in men, and the difference reached statistical significance (Greenblatt et al., 1994). In other studies of sex-dependent differences in kinetics of various CYP3A substrates, significantly higher values of clearance of midazolam, adinazolam, alprazolam, cyclosporine, and tirlizalaz in women compared with men were described (Kristjánsson and Thorsteinsson, 1991; Fleishaker et al., 1992, 1995; Hulst et al., 1994; Gorski et al., 1998; Schroeder et al., 1998; Tsunoda et al., 1999). In a number of reports involving these and other CYP3A substrates (e.g., nefazodone, trazodone, buspirone, and bromazepam), sex-related differences in clearance were not significant (Greenblatt et al., 1983a, 1984, 1987; Ochs et al., 1987; Gammans et al., 1989; Kirkwood et al., 1991; Barbhaiya et al., 1996; Thummel et al., 1996; Kashuba et al., 1998). Thus, the available literature does not support the conclusion that values of clearance of CYP3A substrates are predictably higher in women than in men. Although a trend in this direction is often observed, differences only inconsistently reach significance, suggesting that sex accounts for a relatively small component of the overall variability in clearance of drugs metabolized by CYP3A. When sex-related differences are significant, they generally are applicable to oral administration of high-extraction compounds such as midazolam or triazolam (Gorski et al., 1998). This raises the possibility that the gastrointestinal tract may constitute the principal site for sex-dependent variation in expression and/or activity of CYP3A.

In contrast to triazolam, weight-normalized oral clearance of zolpidem was higher in men than in women; the difference approached but did not quite reach statistical significance. Zolpidem differs importantly from triazolam in its metabolic and pharmacokinetic profile. CYP3A accounts for approximately 60% of zolpidem clearance, with CYP2C9 and CYP1A2 accounting for the majority of the remaining fraction (Pichard et al., 1994; von Moltke et al., 1999). Absolute bioavailability of oral zolpidem averages 70% (Patat et al., 1994). While coadministration of ketoconazole, a relatively specific CYP3A inhibitor, with triazolam greatly reduces triazolam clearance and increases AUC by 5-fold or more, cotreatment of ketoconazole with zolpidem increased zolpidem AUC by a factor of only 1.6 (von Moltke et al., 1996; Greenblatt et al., 1998a,b). Previous studies have not clearly established an effect of sex on zolpidem clearance, but there is a suggestion of higher values of clearance in men as opposed to women (Durand et al., 1992; Salva` and Costa, 1995). The mechanism of the apparently different effects of sex on the kinetic profile of triazolam as opposed to zolpidem is not established but may be related to the contribution of CYP2C9 to zolpidem clearance and the relatively low presystemic extraction of zolpidem.

The single-dose pharmacodynamic profiles of triazolam and zolpidem were similar, based on a variety of well-validated testing procedures. Both compounds produced sedative effects (as rated by subjects themselves and by observers), impairment of performance on the DSST, and increased am-
plitude in the β-frequency range on the EEG. The time course and quantitative intensity of the effects of the two drugs were similar, and for both compounds pharmacodynamic effects were in general indistinguishable from placebo by 8 h after dosing. Furthermore, both triazolam and zolpidem produced anterograde amnesia, characterized mainly by impaired recall of information acquired at or near the time of maximum drug effect. All of these findings are consistent with previous pharmacodynamic studies of these compounds (Berlin et al., 1993; Rush and Griffiths, 1996; Lobo and Greene, 1997; Greenblatt et al., 1998a; Rush, 1998; Rush et al., 1998; Hintzer and Griffiths, 1999). However, on some subjective pharmacodynamic measures, zolpidem showed some unexpected properties, including effects greater than those of triazolam on self-ratings of thinking slowed down and feeling “spacey”. Zolpidem also significantly increased self-ratings of feeling “nervous”, whereas placebo and triazolam were comparable. The mechanism of these apparently different properties of zolpidem, as well as the reason for the two episodes, are not established.

Taken together, the outcome of this and other single-dose pharmacodynamic comparisons of zolpidem with triazolam and other typical full-agonist benzodiazepine receptor ligands suggests that clinical consequences of the apparent receptor subtype selectivity of zolpidem are not established (Lobo and Greene, 1997; Rush, 1998). Similarly, no clear differences emerge between comparable doses of zolpidem and triazolam with respect to hypnotic efficacy or residual effects (Nowell et al., 1997), although some data indicate that zolpidem (at nightly doses of 10 mg or less) is less likely to produce rebound insomnia after discontinuation of treatment than is triazolam at nightly doses of 0.25 mg (Monti et al., 1994; Ware et al., 1997).

An analysis of mean plasma concentrations of triazolam or zolpidem in relation to mean values of pharmacodynamic change scores at corresponding times indicated highly significant relationships predicted on linear or exponential functions. In the case of triazolam, the data were also consistent with an equilibration delay between plasma and the theoretical effect site. This phenomenon has been reported in some previous studies of orally administered triazolam (Greenblatt et al., 1994) but not in others (Greenblatt et al., 1998b). For both zolpidem and triazolam, there was no consistent evidence of a sex-dependent difference in 4-h effect areas or RAUC values for any of the pharmacodynamic variables, nor a difference in the kinetic-dynamic relationships based on mean values at corresponding times. Thus, the data do not indicate any important effect of sex on the pharmacodynamic response to single doses of these two benzodiazepine receptor agonists. However, because individual variability within groups proved to be fairly high, the statistical power of comparisons between male and female subjects was correspondingly low. We cannot rule out the existence of small or subtle sex-dependent differences that would require studies of much larger numbers of subjects to evaluate.

References
Ochs HR, Greenblatt DJ, Friedman H, Burstein ES, Locniskar A, Harmatz JS and...

**Sex-Dependent Effects on Triazolam and Zolpidem**


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