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Research Article

Simultaneous Modeling of the Pharmacokinetic and Pharmacodynamic Properties of Benzodiazepines. II. Triazolam

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This study compares the time course of triazolam effects on psychomotor and cognitive skills with triazolam plasma concentrations in a combined pharmacokinetic-pharmacodynamic (sigmoid-E_{max}) model. Ten male subjects received a single oral dose (1 mg) of triazolam or placebo. The CNS impairment effects were measured by using computerized tracking, body sway, and digit symbol substitution tests, and triazolam plasma concentration was measured by gas chromatography. The drug-induced effect changes lagged behind the plasma drug level changes. The magnitude of the time lag was quantified by the half-time of equilibration between concentrations in the hypothetical effect compartment and the plasma triazolam levels ($t_{1/2}k_{eo}$). Essentially the same $t_{1/2}k_{eo}$ (~6 min) was found for subcritical tracking, body sway, and digit symbol substitution tests. When using the predicted drug concentrations at the effect site, the hysteresis of the plasma concentration-effect disappears, suggesting that the hysteresis is not caused by drug induced tolerance. Moreover, the model allows for estimation of the effect site concentration that causes one-half of the maximal predicted effect (EC_{50}, ~5 ng/ml) which is a measure of an individual's sensitivity to triazolam. On the basis of the EC_{50} values of the effect measures, body sway was slightly less sensitive to triazolam than subcritical tracking and digit symbol substitution tests.

KEY WORDS: triazolam; impairment effect; effect site; pharmacokinetic-pharmacodynamic model.

INTRODUCTION

Benzodiazepines are extensively used as sedative, hypnotic, and anxiolytic agents (1). In spite of extensive research with these compounds, there are only a few studies that correlate the temporal relationship between the plasma levels and the onset and duration of central nervous system (CNS) effects of benzodiazepines (2–11). There is a substantial delay of the equilibrium between plasma concentration and drug effect relationships, as these highly lipophilic compounds readily cross the blood–brain barrier (12); yet the presence of a distinct time lag between changes in the plasma drug level and changes in drug-induced effect has been reported (13,14). Further, the descending limb of the concentration–time curve correlated with the offset phase of the effect–time curve following single doses of benzodiazepines with a short half-life (14–17).

With the use of a pharmacokinetic-pharmacodynamic (PK-PD) model, the relationship between the drug effect and plasma level can be explored even if no immediate equilibrium is established between plasma and effect site drug levels (18). We previously demonstrated, with lorazepam, that data obtained under conditions commonly used in benzodiazepine studies can be analyzed with an appropriate PK-PD model (19).

Triazolam, a triazolo-1,4-benzodiazepine derivative, is used as a hypnotic agent for short-term management of insomnia (20). Absorption of triazolam following oral dosing is rapid and almost complete (20). The peak plasma levels are obtained at 0.5 to 2 hr (20,21). Clinically, a rapid rate of absorption of hypnotics is important for initiating sleep. The elimination half-life of triazolam is short, 2 to 5 hr, in healthy individuals (21–23). Metabolism of triazolam in humans involves hepatic oxidation leading to two major hydroxylated metabolites (alpha-hydroxytriazolam and 4-hydroxytriazolam) that are rapidly glucuronidated and excreted in urine (22). Alpha-hydroxytriazolam (AHT) has pharmacologic activity in humans (24); however, AHT does not seem to contribute much to the overall drug effect, because it reaches peak plasma concentrations of less than 20% of triazolam, and its activity is six times less than the parent drug (9,20). Triazolam is more lipophilic than lorazepam but less than diazepam at physiological pH (25).

The CNS effects of triazolam following drug administration were measured using memory tests, critical flicker fusion thresholds, card sorting tests, digit symbol substitution tests, symbol copying tests, hand–eye coordination tests, body sway tests, etc. Most of these studies did not compare the drug effect with the plasma concentration (9,11,26–28).

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The aim of this study is to evaluate the relationship between triazolam plasma concentration and CNS effects, i.e., impairment on psychomotor coordination and cognitive skills, following oral administration in healthy males using a combined PK-PD model.

MATERIALS AND METHODS

Subject Selection

Ten healthy, nonsmoking males aged 24–29 years (mean, 27 years) and weighing from 72 to 78 kg (mean, 77 kg) participated in this study. All subjects were screened with a physical and psychiatric evaluation, complete blood test (including biochemical and hematological screening profiles, platelet counts), urinalysis, and electrocardiogram, and a history of drug abuse was ruled out. The study protocol and consent form were approved by the Duke University Medical Center Institutional Review Board. The purpose and procedures of the study were explained to the subjects and written, informed consent was obtained. Alcohol and other drugs were excluded 72 hr prior to the study and throughout the study period. Prescription medications were excluded 2 weeks prior to study and throughout the study. All subjects received a standard lunch at the same time on each study day. Water was permitted ad libitum, except for 1 hr after the dose. The subjects were confined to the testing area during each study session and were not permitted to engage in any strenuous activities.

Study Design

Subjects were trained to a plateau level of performance on the tasks in three 2-hr sessions, 1 week prior to the test day to minimize the learning effect. The study was a single-dose, two-way randomized crossover design. Double-blind test sessions were scheduled at 2-week intervals in which subjects received a single oral dose of 5 ml triazolam solution (1 mg triazolam in 5 ml of vehicle, containing methocel 15 cps, benzyl alcohol, sodium chloride, polysorbate 80, and water) or placebo (5 ml of vehicle only) with 200 ml of water following an overnight fast. During the test sessions, the effects of triazolam on several computerized cognitive and neuromotor tasks were measured. EKG and breathing were also monitored, allowing careful status evaluation of the subjects. The dose (1.0 mg) is high for clinical use, however, we did not see any adverse effects or side effects in our healthy subjects.

Each test session started at 8:00 AM with a predrug trial to determine the baseline of the psychomotor and cognitive tasks. Seven milliliters of venous blood samples were drawn into heparinized vacutainers at 0 min (prior to the dosing) and at 10, 15, 20, 35, 55, 80, 95, 110, 155, 185, 240, 315, 330, 365, 380, and 415 min following the dose from an obdurated indwelling catheter in the subjects' left forearm. The blood samples were centrifuged and the plasma was harvested and frozen as soon as possible. Plasma was stored frozen until assayed.

Drug Effect Measurement

The effects of triazolam on cognitive and psychomotor performance were evaluated using continuous subcritical tracking (TRKN), a measure of hand–eye coordination; body sway (SWAY), a measure of ataxia; and digit symbol substitution (DSS), a measure of drug effect on memory and psychomotor speed tests. The tasks were performed for 415 min at approximately the same time as the blood samples were drawn. We briefly describe these three tasks. During the TRKN task, a 3-cm-wide vertical bar was illuminated in the center of a 98 × 128-cm rearview video projection screen and extended down the length of the screen. Throughout the task, a small central portion of the bar moved back and forth across the screen. The subjects turned a car steering wheel to keep the moving bar in the center of the screen for 3 min. During the initial 30 sec, the difficulty of the task increased slowly, then remained unchanged for the final 150 sec. Performance was assessed as the root mean square deviation of the bar from the center.

For the SWAY task, the subject stood on a strain gauge transducer platform with his hands at his sides and focused for 30 sec on a fixed point in front. Gross body movements in the lateral and anterior–posterior directions were analyzed with fast Fourier transforms. Ataxia was quantified by summing frequency power scores below 2.5 Hz obtained for the four directions.

In the DSS task, a row of sequential numbers from 1 to 9 was projected in the upper part of the screen with a symbol positioned directly under each number. The symbols were adapted from the digit symbol substitution subtest of the Wechsler Adult Intelligence Scale Revised (29). As individual symbols appeared below the code table, the subject pressed on a keypad the number above the corresponding symbol in the code table. There were 12 presentations per symbol. Both speed and accuracy were measured. The dependent variable was a composite score computed by dividing the total number of correct responses by the average reaction time of the right answers. In order to determine the relationship between drug levels and degree of impairment, DSS scores under placebo and triazolam treatment were used to calculate the drug effect, $E\%$ = (baseline score − raw score)/(baseline score) · 100%.

Analytical Method

Plasma triazolam concentrations were determined by the gas chromatographic method as described by Greenblatt *et al.* (30) with the following modification. The column (0.9 m × 2-mm ID) was packed with 3% SP-2250DB on 100- to 120-mesh supelcoport. Operating temperatures were column, 255°C, detector, 330°C, and injection port, 260°C. Toluene was substituted for benzene as the solvent. The lower limit of sensitivity was 0.25 ng/ml and the interassay coefficient of variation was about 5%.

Pharmacokinetic Analysis

Individual plasma triazolam concentration–time data were analyzed using both compartmental and noncompartmental methods. For the compartmental analysis, the compartmental configuration and the initial estimates of the parameters were determined by JANA (31). The iterative weighted nonlinear least-squares regression program NONLIN (32) was then used to refine the parameter values. The

equation of a two-compartment model with first-order absorption rate (k_a) and a lag time (t-lag) was used to describe triazolam pharmacokinetics for subjects 7 and 9, and the equation of a one-compartment model with first-order absorption rate and a lag time was used to describe triazolam pharmacokinetics for the remaining eight subjects. The alternative pharmacokinetic models (one-compartment vs two-compartment model) for subjects 7 and 9 were compared according to the Akaike information criterion (AIC): $AIC = N \cdot \ln(WSS) + 2p$, where N is the number of data points, WSS is the weighted sum of deviations squared, and p is the number of parameters estimated (33). The pharmacokinetic model with minimum AIC is regarded as the best representation of the plasma concentration–time course data. The estimates were obtained of the k_a, the t-lag, the rate constants for a relatively rapid decay (λ_1) and a slower decay or terminal elimination rate constant (λ_2), and their corresponding intercepts. The area under the plasma concentration–time profile to the last time point (AUC_t) was estimated by trapezoid rule. The total area under the plasma concentration time curve (AUC) was calculated by adding AUC_t, and the residual area calculated by C_t/λ_2, where C_t is the plasma level at the last time point at which the concentration is determined. The oral clearance (CL/F), the half-lives ($t_{1/2}k_a$, $t_{1/2}\lambda_1$, and $t_{1/2}\lambda_2$), the apparent volume of distribution (V_1/F), the peak plasma level (C_{max}), and the time to reach C_{max} (t_{max}) were calculated in the usual manner (34).

Pharmacokinetic-Pharmacodynamic Analysis

Plots of plasma triazolam concentration versus measured CNS impairment effect (TRKN, SWAY, and DSS) showed counterclockwise hysteresis, indicating that the site of action of triazolam (a) is kinetically distinguishable from the plasma compartment and (b) contains a distinct time lag between changes in the plasma concentration and changes in CNS effects.

A compartmental model approach (parametric) was used to characterize simultaneously the pharmacokinetics and pharmacodynamics of triazolam. Using a one-compartment (and two-compartment for two subjects) pharmacokinetic model for the description of plasma triazolam concentration and an equilibration rate constant (k_{eo}) which controls the rate of drug loss from the effect compartment by first-order process, an expression describing the time course of the effect site concentration (C_e) was derived (35). The function for the effect compartment concentration was used with a sigmoid-E_{max} model to predict the effects (E) of TRKN and SWAY:

$$E = E_o + (E_{max} \cdot C_e^\gamma)/(EC_{50}^\gamma + C_e^\gamma) \quad (1)$$

In this equation, E_{max} is the maximum change in predicted response which can be produced by the drug, E_o is the baseline effect (or placebo effect), EC_{50} is the concentration at the effect site causing 50% of E_{max}, and γ is the Hill coefficient (or slope factor) which determines the sigmoidicity of concentration-effect curve. The DSS data were fitted according to Eq. (2):

$$E\% = (E_{max} \cdot C_e^\gamma)/(EC_{50}^\gamma + C_e^\gamma) \quad (2)$$

Both equations assume that the C_e elicits the effect (impairment) according to the Hill equation. These effect–site drug concentration–effect relationships were chosen because (a) they were in accordance with the law of mass action and general receptor theory and the parameters, EC_{50} and E_{max}, bear pharmacological meaning (18), and (b) these models [Eqs. (1) and (2)] described the data better than other models, e.g., the linear or gamma-linear or simple-E_{max} model.

The pharmacodynamic parameters (EC_{50} and k_{eo}) for the three different measures of the CNS effect were compared with a one-way ANOVA (36). Values of $P < 0.05$ were considered statistically significant. For nonlinear relationships, r^2 and r (and the estimate of error SD) values were obtained by JANA and NONLIN, respectively, and for model selection, AIC values were compared.

RESULTS

Pharmacokinetics

The plasma triazolam concentration–time profiles of subjects 7 and 9 were best characterized by a two-compartment model and the plasma triazolam concentration time profiles of the remaining 8 subjects were best characterized by a one-compartment model with first-order absorption and lag time. Figure 1 shows an example (subject 3) of the observed plasma concentration–time profile and the theoretic curve generated from NONLIN-estimated parameters. When the plasma concentration–time data of subjects 7 and 9 were fitted to both one- and two-compartment models, the two-compartment model yielded lower AIC values (see Table I). Both compartmental and noncompartmental methods were used to obtain the parameter estimates given in Table I.

Pharmacodynamics

The relationship between predicted and measured CNS

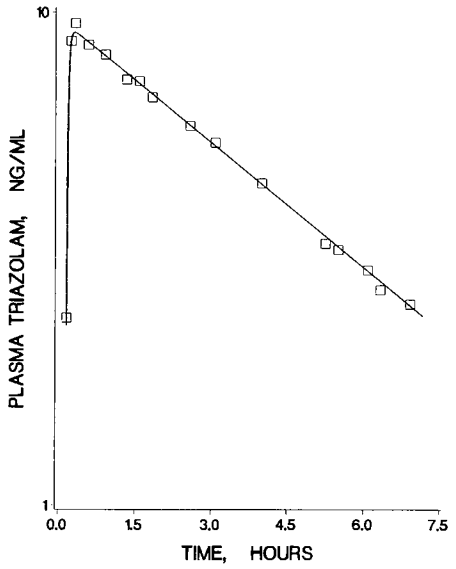

Fig. 1. Plasma concentration–time profile of triazolam following oral administration of triazolam to subject 3. The symbols represent the observed concentrations and the solid line represents the theoretic line obtained by the curve-fitting procedure.

Table I. Pharmacokinetics of Triazolam

Subject	Parameter									
	$t_{1/2}k_a$ (hr)	$t_{1/2}\lambda_1$ (hr)	$t_{1/2}\lambda_2$ (hr)	t-lag (hr)	C_{max} (ng/ml)	t_{max} (hr)	V_1/F (L)	CL/F (L/hr)	r	S^a
1	0.080	—	3.08	0.18	9.98	0.66	100.90	22.70	0.955	0.58
2	0.043	—	3.96	0.22	7.30	0.60	130.43	22.83	0.985	0.30
3	0.038	—	3.48	0.15	9.50	0.40	105.74	21.06	0.972	0.41
4	0.200	—	3.41	0.10	7.22	0.96	135.92	27.62	0.981	0.37
5	0.320	—	2.38	0.19	5.23	1.26	145.14	42.26	0.990	0.14
6	0.070	—	4.80	0.16	8.85	0.58	137.25	19.80	0.930	0.60
7[b]	0.029	0.16	3.33	0.18	6.30	0.38	121.82	27.04	0.987	0.27
8	0.350	—	2.64	0.14	7.10	1.20	145.73	38.25	0.978	0.34
9[c]	0.030	0.12	5.02	0.10	6.40	0.30	129.04	18.32	0.970	0.45
10	0.300	—	1.95	0.14	6.80	0.95	119.67	42.54	0.964	0.51
Mean	0.064[d]		3.15[d]	0.16	7.47	0.83	127.16	25.84[d]	0.971	0.41
±SD	±0.02		±0.03	±0.04	±1.51	±0.32	±9.86	±2.37	±0.018	—
SE[e] range	(0.02–0.24)	(0.07–0.10)	(0.09–0.49)	(0.02–0.06)	(0.17–0.73)	(0.10–0.28)	(5.90–10.7)			

[a] Estimate of error standard deviation = $[RSS/(n - m)]^{1/2}$, where RSS is the residual sum of squares, n is the number of data points, and m is the number of parameters.
[b] AIC values: one-compartment model (46.6) vs two-compartment model (36.4).
[c] AIC values: one-compartment model (50.9) vs two-compartment model (41.7).
[d] Harmonic mean ± jackknife standard deviation (37).
[e] Model determined standard error of each parameter estimate.

effects (TRKN, SWAY, and DSS) versus plasma concentration in subject 3 is illustrated in Fig. 2. Similar curves using measured and predicted effect, TRKN, SWAY, and DSS values, versus effect compartment triazolam concentration are shown in Fig. 3. The points are joined in time sequence by the dashed line starting in the lower left corner. The counterclockwise hysteresis loops in Fig. 2 indicate the need for an effect compartment model to account for equilibration between plasma and the effect site. The solid lines in each figure show the effects predicted by the PK-PD model as a function of the plasma and effect compartment triazolam concentrations. The pharmacodynamic parameter estimates of TRKN, SWAY, and DSS are given in Table II.

The EC_{50} of SWAY appeared to be larger than those of TRKN and DSS but the differences were not statistically significant. No significant differences were found with respect to the mean k_{eo} values of 6.83 hr^{-1} for TRKN, 6.67 hr^{-1} for SWAY, and 6.23 hr^{-1} for DSS, respectively.

DISCUSSION

The pharmacokinetic parameters given in Table I describe triazolam as a drug with a very rapid absorption phase followed by a rapid elimination phase. We found in two subjects that it also has a rapid distribution phase. The distribution half-lives ($t_{1/2}\lambda_1$s) are similar to those previously reported (14). The short absorption half-life ($t_{1/2}k_a$), t-lag, and t_{max} represent fast absorption of triazolam from a solution formulation. However, our mean t_{max} value of 0.83 hr, with a range of 0.3–1.26 hr, is similar to reported t_{max} values, 0.5–2 hr (21), 0.98 hr (22), and 0.25–3 hr (38), in which a compressed tablet dosage form was used. Our findings of a large interindividual variation in triazolam $t_{1/2}k_a$, t-lag, and t_{max} are also consistent with previous observations made following oral administration of triazolam (21,38,39). The mean elimination half-life ($t_{1/2}\lambda_2$) and clearance (CL/F) values are similar to those reported previously from studies in young normal volunteers (38–41). Clearance and $t_{1/2}\lambda_2$ varied among individuals more than twofold, indicating individual differences in oxidative biotransformation. The apparent volume of distribution of triazolam was larger than the subjects' body weight (mean, 77 kg). Consistent with an earlier report (42), the finding that the drug has a relatively large apparent volume of distribution is indicative of significant tissue uptake of triazolam.

Good fits of the plasma concentration–time data with the pharmacokinetic model were obtained for all 10 subjects as indicated by their individual "r" value and estimates of standard deviation. Since pharmacokinetic parameters estimated for each subject were then used for fitting the measured CNS effect data with the proposed PK-PD model, the selection of the appropriate pharmacokinetic model to characterize the plasma triazolam–time data is important.

Several reported studies have measured the drug effect in humans following triazolam administration but most of these investigators did not compare the effect with plasma triazolam levels (9,11,26–28). Although a few studies are presently available on the relationship between the plasma level and the effect of triazolam (14–17), the termination of effect is related to the postdistribution phase (or elimination phase) of plasma triazolam–time data, thus not taking hysteresis into account, even though peak effects appeared after the peak plasma triazolam concentration (14). Plasma triazolam level–effect plots (TRKN, SWAY, and DSS) of all our 10 subjects demonstrate a counterclockwise hysteresis, indicating that an effect compartment is needed for the PK-PD model (18,43) (Fig. 2).

The model demonstrates the presence of a distinct equilibration time lag ($t_{1/2}k_{eo}$) between the plasma drug level and the measured effects in all subjects. The large interindividual

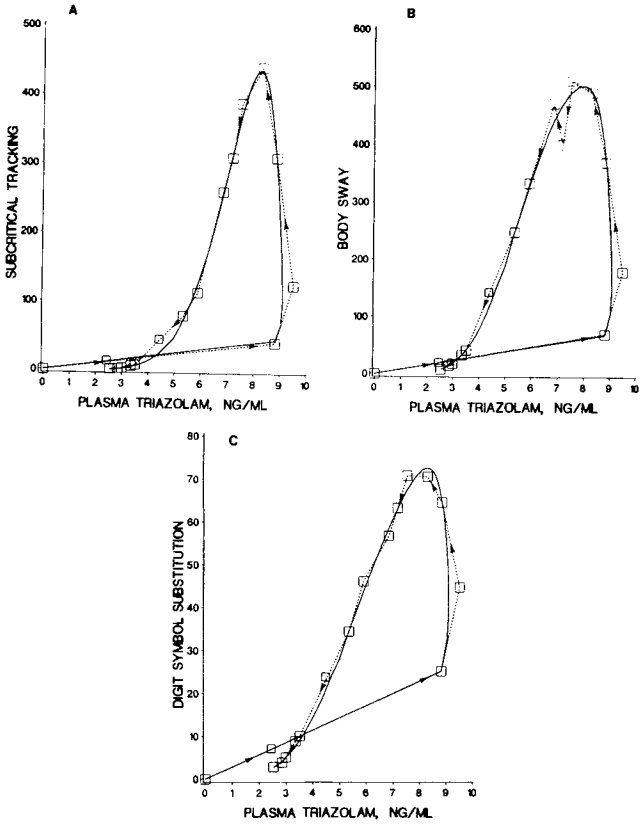

Fig. 2. Measured subcritical tracking (A), body sway (B), and digit symbol substitution (C) versus plasma triazolam concentration data in subject 3. The first observations were made before dosing and the sequence of observations proceeds in a counterclockwise direction, causing hysteresis loops. The symbols are the actual data and the solid lines are the effect–concentration curve predicted by the PK-PD model.

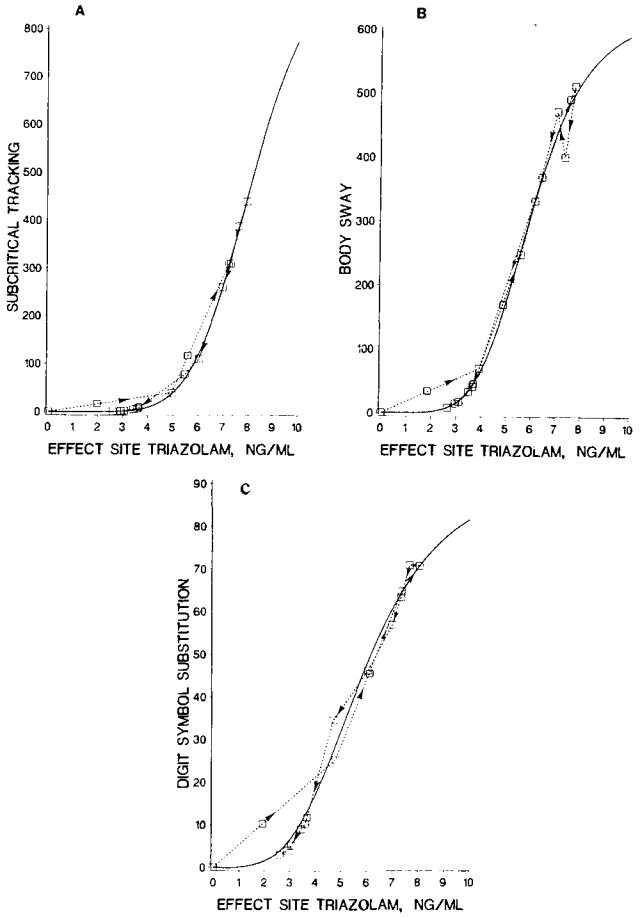

Fig. 3. Measured subcritical tracking (A), body sway (B), and digit symbol substitution (C) versus predicted effect site triazolam concentration data in subject 3. The hysteresis loops have been collapsed by accounting for the rate of equilibration between plasma and the effect site. The symbols are the actual data and the solid lines are the effects predicted by the PK-PD model as a function of the predicted effect site triazolam concentrations.

variability of $t_{1/2}k_{eo}$ (Table II) may be due to differences in triazolam disposition among the subjects, as the magnitude of the k_{eo} is determined by the cerebral perfusion, brain: blood partitioning, diffusion through blood:brain barrier, and postreceptor events (18). In spite of this variability our results demonstrate essentially the same mean $t_{1/2}k_{eo}$ for the different measures of CNS effect. The model is also capable of relating the pharmacokinetic half-lives ($t_{1/2}\lambda_1$ and λ_2) of triazolam to its pharmacodynamic half-life ($t_{1/2}k_{eo}$). The assumption that the observed effects are related to the central compartment appears to be valid, as shown by the interrelationship of the pharmacokinetic $t_{1/2}s,\lambda_1$ and λ_2, and $t_{1/2}k_{eo}$ (44). Tables I and II show that the $t_{1/2}k_{eo}$ for all three tasks for subjects 7 and 9 are smaller than the plasma distribution half-life, $t_{1/2}\lambda_1$, and the terminal elimination half-life, $t_{1/2}\lambda_2$, indicating that the equilibration with the effect compartment is rapid relative to the changes in the central compartment. This rapid equilibrium ensues a fast onset of triazolam effect and the effect declines in parallel with its plasma concentration–time curve. For the remaining eight subjects $t_{1/2}k_{eo}$ for all three tasks are also smaller than their $t_{1/2}\lambda_2$, indicating that the dissipation of drug effect declines in parallel with its plasma concentration–time curve. Because of the above reasons Baktir *et al.* (17) could correlate the plasma elimination phase directly with the effect offset phase of triazolam.

The predicted effect site triazolam concentration and effect plots (Fig. 3) show the hysteresis loop has collapsed by accounting for the rate of equilibration between the plasma and the effect compartments. The ability of the effect compartment model to collapse the hysteresis loop supports the assumptions for a rapid equilibration existing between the drug concentration in the brain and at the benzodiazepine receptor site (43). It also provides circumstantial evidence against a time-dependent change in the properties of the receptor that is found with benzodiazepines manifesting marked acute tolerance (45). In agreement with this result, no evidence of acute tolerance was previously observed following a single i.v. dosing (dose ranged from 0.125 to 1.0 mg) or multiple oral dosing (up to 3 mg) of triazolam (14,46).

The parameters, EC_{50} and E_{max}, estimate the benzodiazepine receptor's sensitivity to triazolam, EC_{50}, and the predicted maximal responsiveness, E_{max}, based upon the PK-PD modeling. Although the mean values of EC_{50} are

Table II. Pharmacodynamics of Triazolam

Parameters	Measured effects		
	TRKN	SWAY	DSS
k_{eo} (hr^{-1})	6.83 ± 2.72 (2.04–9.24)	6.67 ± 2.52 (2.89–9.00)	6.23 ± 2.73 (2.39–9.12)
$t_{1/2}k_{eo}$ (hr)[a]	0.099 ± 0.034 (0.075–0.34)[b]	0.104 ± 0.05 (0.077–0.24)	0.111 ± 0.04 (0.076–0.29)
EC_{50} (ng/ml)	4.79 ± 1.87 (2.96–8.17)	5.55 ± 1.58 (3.59–8.30)	4.08 ± 2.01 (2.60–8.61)
E_{max}	566.80 ± 197.48 (393.86–990.51)	755.53 ± 122.69 (579.74–900.64)	81.35 ± 20.11 (50.60–106.10)
γ	5.78 ± 0.79 (4.45–6.54)	4.52 ± 1.41 (2.31–6.61)	3.72 ± 1.22 (2.61–6.54)
E_0	13.19 ± 2.27 (9.67–16.02)	12.94 ± 2.77 (9.53–17.88)	—
r	0.946 ± 0.029 (0.912–0.988)	0.937 ± 0.031 (0.904–0.973)	0.958 ± 0.024 (0.916–0.988)

[a] Harmonic mean ± jackknife standard deviation.
[b] Range (n = 10).

similar for all three tasks, the SWAY task is a slightly less sensitive measure of triazolam effects than TRKN and DSS, with DSS the most sensitive. In our previous report (19) the mean EC_{50} value, derived from all three tasks, for lorazepam was 31.67 ng/ml, versus 4.8 ng/ml for triazolam in our present study, indicating that lorazepam is seven times less potent than triazolam. This finding agrees with the reported dose potency relationship between triazolam and lorazepam, i.e., triazolam is eight times more potent than lorazepam (47). The equilibration time lag found with lorazepam (0.5 hr), in our previous study (19), was approximately five times greater than that of triazolam (0.11 hr), indicating that for a given plasma level, effect onset and termination are much more rapid for triazolam than for lorazepam. The interindividual differences between E_{max} for TRKN, SWAY, and DSS are not always consistent with the mean values, probably because of differences among individuals in the receptor's sensitivity to the drug.

The E_{max} model is compatible with a receptor binding and occupancy model (48). The EC_{50} and E_{max} parameters can be used to examine how an altered physiological condition (e.g., aging) or pathological state might affect the receptor sensitivity to triazolam. The slope factor (γ) is used mostly in an empirical way with no specific mechanistic implications (35,43,49). The values for all three tasks describe a relatively steep plasma concentration-effect relationship. Steep concentration–effect relationships ($\gamma > 3$) also have been reported for diazepam and midazolam (50).

This investigation has addressed the suitability of the described PK-PD model to establish a quantitative relationship between the plasma concentration–CNS effect relationship of triazolam. The impairment effects of triazolam following oral administration are characterized by a hysteresis that differs between subjects. The use of the combined PK-PD model has the potential to provide information on individual and group pharmacokinetic and pharmacodynamic parameters. Such an approach can be used to determine whether conditions such as aging decreases triazolam dose requirements (due to change in the receptor's sensitivity to triazolam) and whether altered dose requirements can be attributed to changes in pharmacokinetics, pharmacodynamics or both.

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