Simultaneous modeling of the pharmacokinetics and pharmacodynamics of midazolam and diazepam

The pharmacokinetics and pharmacodynamics of midazolam and diazepam were compared after intravenous infusions of 0.03 and 0.07 mg/kg midazolam and 0.1 and 0.2 mg/kg diazepam on four separate occasions in 12 healthy male subjects in a randomized four-way crossover design. The Digit Symbol Substitution Test (DSST) was used as a measure of drug effect. Subjects performed three practice tests before dosing to account for any effects caused by familiarization ("learning curve") with the testing procedure. Pharmacokinetic and pharmacodynamic data were simultaneously fitted to a semiparametric model. In this model, a pharmacokinetic model related dose to plasma concentrations, a link model related plasma concentrations to the concentration at the effect site, and a pharmacodynamic model related the effect site concentration to the observed effect. The plasma–effect site equilibrium half-life was approximately 2½ times longer for midazolam than for diazepam, which is in good agreement with previously published data. Based on the estimated effect site concentration at which half of the maximal effect was reached, midazolam had approximately a sixfold greater intrinsic potency than diazepam. This difference in potency was also observed in a previous study that used transformed electroencephalographic (EEG) data to assess pharmacodynamic activity. The findings reported here with a clinically relevant pharmacodynamic marker (DSST) confirm the utility of surrogate drug effect measures such as EEG. This work also shows the feasibility of conducting pharmacokinetic pharmacodynamic analysis during the drug development process. (CLIN PHARMACOL THER 1995;58:35-43.)

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When appropriate, pharmacokinetic-pharmacodynamic analysis is performed by correlating drug effect with plasma concentration, with the lag-time between concentration-time curve and effect-time curve (hysteresis) being described by the equilibrium rate constant (k_{eo}).[1] The reasons for lag-time in a direct effect model may include the movement of the drug from the blood through physiologic barriers, such as the blood-brain barrier, and the interaction between the drug and its receptor.

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Received for publication Aug. 12, 1994; accepted Jan. 16, 1995.

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0009-9236/95/$3.00 + 0 **13/1/63528**

It has been suggested that it may take slightly longer for an "effect-equivalent" dose of midazolam to show pharmacologic activity when compared with diazepam. Previous data indicate that the k_{eo} half-life ($t_{½}k_{eo}$) for midazolam is greater than that for diazepam when electroencephalographic (EEG) activity is used as the pharmacodynamic end point.[2] Although this finding supports clinical observations, a correlation between EEG activity and more common parameters (i.e., psychomotor performance) has not been shown for midazolam. However, there is good correlation with other compounds, such as triazolam and alprazolam.[3,4]

In this study, a fairly simple psychometric task, the Digit Symbol Substitution Test (DSST),[5] was used to assess the pharmacodynamic activity of both compounds. The DSST is a sensitive measure of rapid drug-induced changes in psychometric performance.[6] This study was designed to use a clinical parameter such as DSST to support the pharmacodynamic find-

ings in other studies in which only EEG activity was used.

METHODS

Conduct of study. Twelve male subjects (age range, 19 to 34 years; weight range, 80 ± 4 kg) completed the study. All subjects were healthy ambulatory adults who had no clinical evidence of significant major organ disease, based on physical and laboratory evaluations. The protocol was approved by the Newark Beth Israel Medical Center Review Committee, and all subjects gave written informed consent to all procedures.

This study was conducted according to a four-way randomized crossover design with use of a third-party blinding procedure. A minimum 1-week washout period separated each treatment. The use of alcohol and any medications was prohibited for 48 hours before each treatment period. Intake of caffeine-containing food or beverages was prohibited for 8 hours before and 4 hours after each drug administration.

After admission to the study unit on the evening before each dosing interval, subjects performed three 5-minute practice DSSTs. In the morning, a 5-minute baseline DSST was conducted 30 minutes before dosing. Subjects were then administered, in a blinded manner, either 0.03 mg/kg midazolam, 0.07 mg/kg midazolam, 0.10 mg/kg diazepam, or 0.20 mg/kg diazepam according to a randomized schedule. Dosages of each test medication were prepared by an unblinded third party and were calculated on the basis of the subject's weight at the time of each admission to the study unit. To attempt to equalize dosage volumes, the midazolam doses were diluted with sterile normal saline solution to a volume equivalent to that of the 0.20 mg/kg diazepam dose. Because of the nature of the diazepam formulation, the volume of the 0.10 mg/kg diazepam dose was not adjusted. For each dose, the syringe and delivery tubing were covered so that the identity of the test substance was not disclosed. Each treatment was administered as a 90-second continuous injection through an intravenous catheter with use of a syringe infusion pump.

Sixty seconds before initiation of the dose, subjects began the first treatment DSST. The first treatment DSST lasted for 10 minutes or until the subject was too sedated to continue. The number of correct substitutions completed during each 20-second interval were counted and recorded. Subsequent 5-minute DSSTs were conducted at 30, 60, 90, 120, and 180 minutes after initiation of the injection. DSST recordings were then normalized to 1-minute intervals for comparative analysis.

Assay of samples. Blood samples (5 ml) for determination of plasma benzodiazepine concentrations were collected by means of an indwelling catheter positioned distal to the infusion line. Samples were collected immediately before initiation of the first treatment DSST (0 hour, predose) and at ½, 1, 1½, 2, 2½, 3, 3½, 4, 5, 6, 8, 10, 20, 40, 60, 90, 120, and 180 minutes after drug administration. Samples during the first 10 minutes after administration were collected over 25 seconds at the rate of 1 ml/5 sec, with the sample collection time being the midpoint of the collection period (i.e., collection for the ½-minute sample began at 15 seconds and ended at 40 seconds). The remaining samples were collected at the actual time indicated above. Samples were immediately transferred into heparinized Vacutainer tubes (Becton-Dickinson Vacutainer Systems, Franklin Lakes, N.J.) and centrifuged, and the plasma was stored at −20° C until analysis.

Plasma benzodiazepine concentrations were determined by specific gas chromatography/negative chemical ionization mass spectroscopy (GC/NCIMS) methods. Midazolam and 1-hydroxymethylmidazolam concentrations were measured by addition of deuterated analogs of each compound to the plasma as reference standard. The plasma was adjusted to pH 10 with the addition of a saturated borate solution, then extracted with toluene that contained 30% dichloromethane. The residue was reconstituted in 50 μl bistrimethytrifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS), and an aliquot analyzed by GC/NCIMS. The limit of quantitation for midazolam and its metabolite were 1.1 ng/ml and 0.1266 ng/ml, respectively, with use of 1.0 ml plasma. Concentrations of the 1-hydroxymethylmidazolam metabolite were generally low or below measurable limits for all subjects.

A deuterated analog of diazepam was added to the plasma as a reference standard. Plasma was adjusted to pH 9 by the addition of 1.0 mol/L sodium borate buffer. Compounds of interest were extracted into toluene (80)/heptane (20). After evaporation of the organic layer under nitrogen, the residue was reconstituted in 50 μl methanol. An aliquot was analyzed with use of GC/NCIMS. The limit of quantitation of the assay was 2 ng/ml with use of 1.0 ml plasma.

Pharmacodynamic and pharmacokinetic analysis. Data from this study were analyzed using a semiparametric approach. This method has shown good success in the literature,[7,8] and the results equate well with those determined by more traditional approaches.[2]

Semiparametric analysis. The value of k_{eo} was determined for each subject by simultaneously fitting the pharmacokinetic and pharmacodynamic data to a

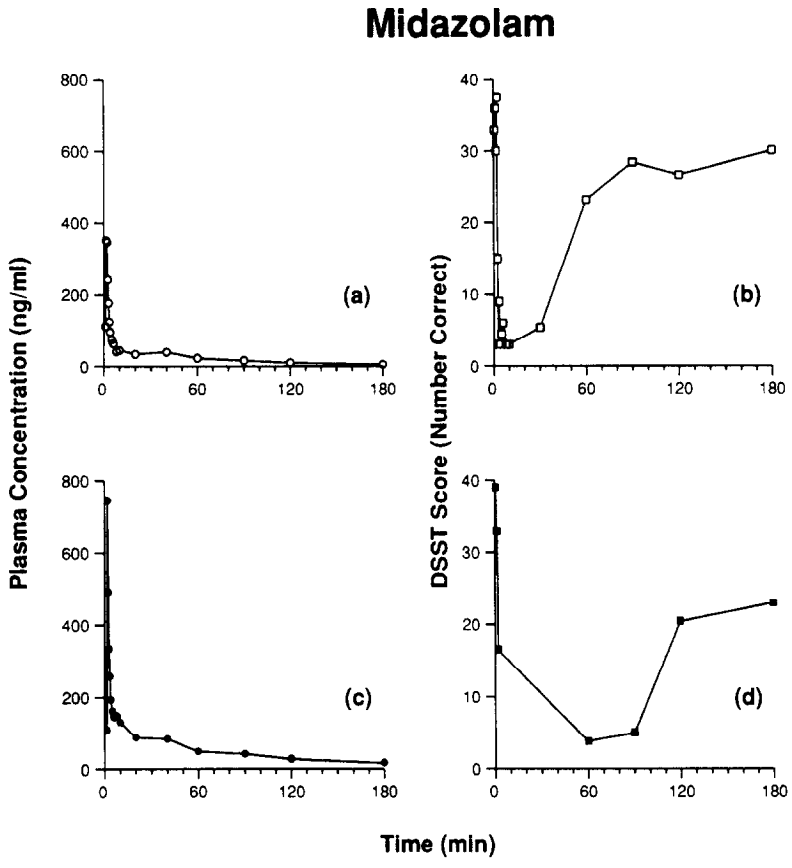


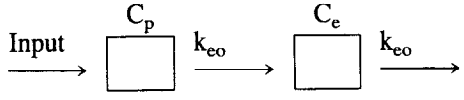
Fig. 1. Plasma concentration versus time (*open circles*, low dose; *solid circles*, high dose) and effect (Digit Symbol Substitution Test [DSST] score) versus time (*open squares*, low dose; *solid squares*, high dose) in subject 6 after 0.03 mg/kg midazolam and 0.07 mg/kg midazolam.

semiparametric model. In general, a biexponential pharmacokinetic model related dose to plasma concentrations (C_p), a link model related C_p to the concentration at the effect site (C_e), and a pharmacodynamic model related C_e to the effect. Both the pharmacokinetic and pharmacodynamic models were nonparametric, but the link model was parametric.

In the pharmacokinetic model, C_p was determined as a biexponential function:

$$C_p = \sum_{i=1}^{n} A_i e^{-\lambda_i t} \quad (n = 2)$$

C_e was given by the convolution of drug concentration at the venous site (C_p) with a monoexponential function with exponent k_{eo}, as is shown in the diagram below:



The rate constant of transfer into the effect site (k_{eo}) is assumed to be equal to the rate constant out of the effect site.

The rate of transfer of drug into the effect compartment is described by the following differential equation:

$$\frac{dC_e}{dt} = k_{eo}(C_p - C_e)$$

For each k_{eo}, C_e is computed by the following:

$$C_e = k_{eo} C_p * e^{(-k_{eo}t)}$$

in which the asterisk (*) indicates the convolution operator.

The pharmacodynamic model relating effect (E) to C_e was an arbitrary nonparametric function of C_e:

$$E = E_0 + \frac{E_{max} C_e}{EC_{50} + C_e}$$

in which E_{max} is the maximum effect achieved, EC_{50} is the effect site concentration at which half of E_{max}

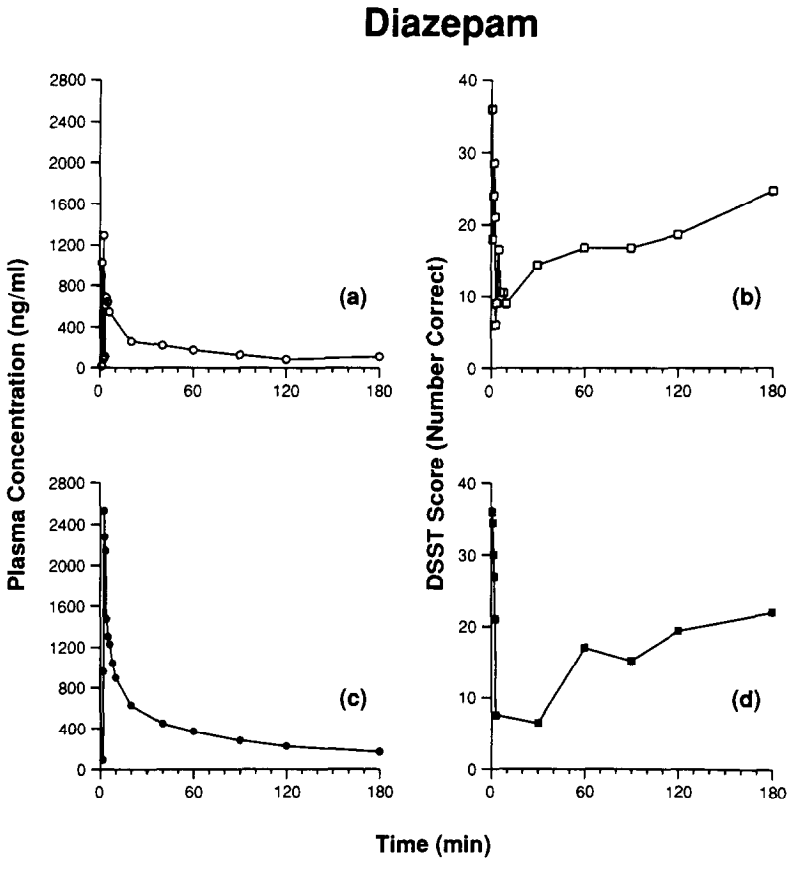


Fig. 2. Plasma concentration versus time (*open circles*, low dose; *solid circles*, high dose) and effect (DSST score) versus time (*open squares*, low dose; *solid squares*, high dose) in subject 6 after 0.03 mg/kg midazolam and 0.07 mg/kg midazolam and after 0.1 mg/kg diazepam and 0.2 mg/kg diazepam.

was reached, and E_0 is the baseline effect, which may be affected by repeat testing. For the purposes of this analysis, E_{max} was defined as the complete inability to score any correct DSSTs (100% inhibition). Because subjects performed several practice DSSTs before dosing, the learning curve was assumed to be completed or maximized during these practice sessions; therefore changes in the baseline effect value (E_0) were not considered in this model (0% inhibition at baseline).

After the computation of C_e and E, the objective function, defined as the weighted difference between the estimated and predicted E values, was evaluated and minimized as a measure of the hysteresis loop E versus C_e connected in time order.

For each subject, the observed percent of maximal effect achieved for each treatment was calculated and plotted versus the predicted C_e. E_{max} was read directly from the plot of E versus C_e. The EC_{50} for each subject was either read directly from the data file or interpolated from the data available. The $t_{1/2}k_{eo}$ was calculated as follows:

$$t_{1/2}k_{eo} = \frac{\ln(2)}{k_{eo}}$$

Initial estimates of k_{eo} were determined nonparametrically[9] and refined in the modeling process.

Noncompartmental pharmacokinetic analysis. For both drugs, the maximum plasma concentration (C_{max}) and time of maximum concentration (t_{max}) were read directly from the concentration-time data. The elimination rate constant (β) for midazolam was calculated by fitting the individual data from the terminal portion of the concentration-time profile by a log-linear regression equation with use of the method of least squares. The corresponding elimination half-life ($t_{1/2}$) was calculated as follows:

$$t_{1/2} = \frac{\ln(2)}{\beta}$$

The area under the midazolam concentration-time curve from time 0 to infinity [AUC(0−∞)] was deter-

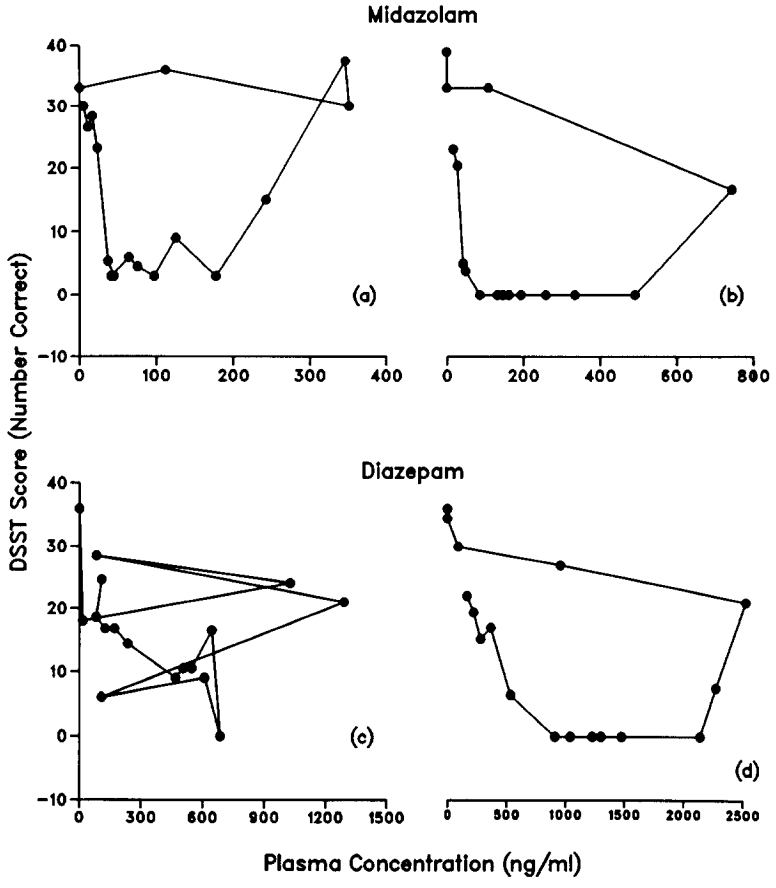


Fig. 3. Plasma concentration versus effect (DSST score) in subject 6 after 0.03 mg/kg midazolam **(a)**, 0.07 mg/kg midazolam **(b)**, 0.1 mg/kg diazepam **(c)**, and 0.2 mg/kg diazepam **(d)**.

mined by standard trapezoidal summation and extrapolation techniques. The systemic clearance (CL) was determined by division of the dose by AUC, and the apparent volume of distribution (Vd_β) was calculated by division of CL by β.

The area under the diazepam concentration–time curve from time 0 to the last measurable concentration [AUC(0−t)] was determined by trapezoidal summation. Because the elimination $t_{1/2}$ of diazepam has been documented as ranging between 24 and 50 hours, the elimination rate constant for this compound could not be determined from the data available in this study because the duration of sampling (3 hours after dosing) was not sufficient to accurately characterize the terminal elimination phase for diazepam. Therefore, values for $t_{1/2}$, CL, and Vd_β could not be calculated for this compound.

RESULTS

Plots of both plasma concentration versus time and effect versus time curves for midazolam for subject 6 are shown together in Fig. 1. Plots of plasma concentration versus time and effect versus time curves for diazepam for this subject are shown in Fig. 2. Fig. 3 displays the hysteresis loops that were generated when observed plasma concentration was plotted versus effect for the same subject. The collapsed loops that resulted after prediction of the effect site concentration and determination of k_{eo} for subject 6 are shown in Fig. 4. The portion of the collapsed loop that generally reaches a plateau was taken to be E_{max}. Seven of 12 subjects achieved 100% of E_{max} after the higher midazolam and diazepam doses were administered.

Mean values for k_{eo}, E_{max}, and EC_{50} and harmonic mean values of $t_{1/2}k_{eo}$ for each midazolam dose (0.03 and 0.07 mg/kg) and the two doses together, as well as for each diazepam dose (0.1 and 0.2 mg/kg) and the two doses together, are summarized in Table I. The harmonic mean $t_{1/2}k_{eo}$ for the pooled high and low midazolam doses was 3.2 minutes, approximately 2½ times slower than that for the pooled diazepam doses (1.2 minutes). The mean EC_{50} after the higher doses was determined to be 20.9 ng/ml for midazolam and 132 ng/ml for diazepam. Values for the effect param-

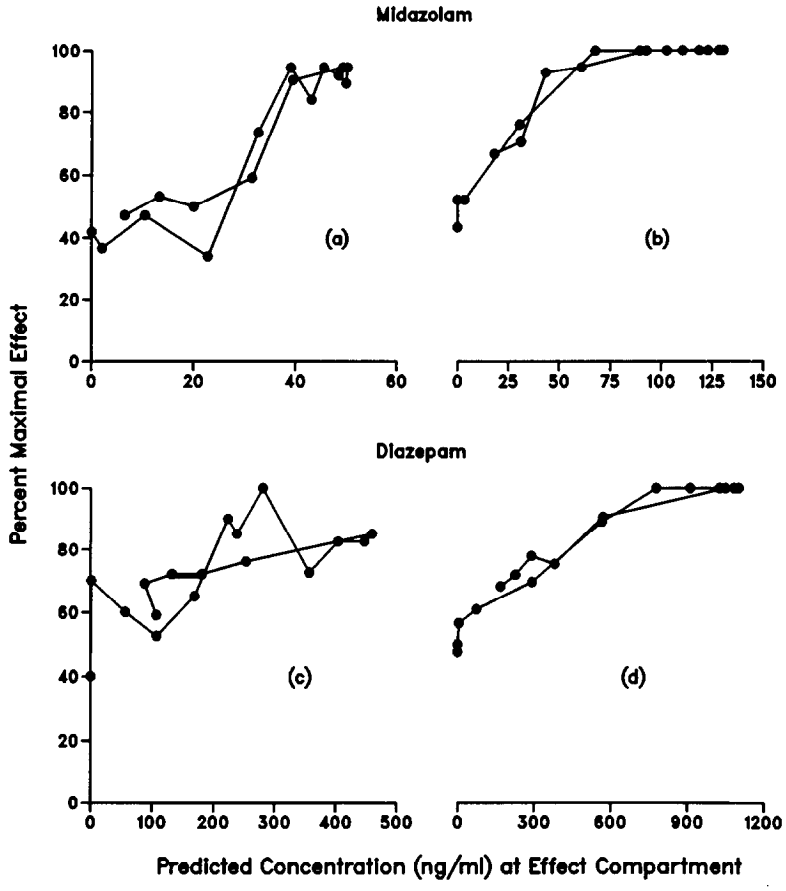


Fig. 4. Percent maximal effect versus predicted concentration at the effect site after determination of k_{eo} and collapse of the hysteresis loop in subject 6 after 0.03 mg/kg midazolam (**a**), 0.07 mg/kg midazolam (**b**), 0.1 mg/kg diazepam (**c**), and 0.2 mg/kg diazepam (**d**).

eters after the high and low doses for each drug were averaged together. The mean EC_{50} value for the midazolam doses was 18.1 ng/ml and 116 ng/ml for the diazepam doses. Based on a comparison of the estimated EC_{50} values, midazolam is on average 6 times more potent than diazepam.

Mean pharmacokinetic parameters for midazolam and diazepam are given in Table II. Mean C_{max} values of midazolam were 0.28 and 0.53 μg/ml for the 0.03 and 0.07 mg/kg doses, respectively. Harmonic mean elimination $t_{1/2}$ values were 1.1 and 1.3 hours, respectively. The 0.03 and 0.07 mg/kg midazolam doses were cleared at mean rates of 12.4 and 9.4 ml/min/kg, respectively. Midazolam has a large Vd_β, with mean values in this study of approximately 1 L/kg for both doses.

Mean C_{max} values of diazepam were 1.12 and 2.39 μg/ml for the 0.1 and 0.2 mg/kg doses, respectively. As a result of insufficient sampling for pharmacokinetic analysis, the elimination $t_{1/2}$ of diazepam and the drug's CL and Vd_β could not be determined and are not reported here.

DISCUSSION

For both midazolam and diazepam, the DSST appeared to be a good parameter for assessment of pharmacodynamic activity. The results of the semiparametric modeling with use of the DSST data indicated that a much greater level of sedation was achieved with the administration of a higher dose for both drugs, as anticipated. With these higher doses, the effect generally reached a plateau (E_{max}). Values that indicate that the E_{max} was achieved were generated for more than 70% of the subjects who received either drug. However, at the lower doses, only one (diazepam) and four (midazolam) subjects achieved >95% of the E_{max}. Because a plateau was generally reached at the higher doses, an estimate of the intrinsic po-

Table I. Pharmacodynamic parameters after intravenous infusions of 0.03 mg/kg and 0.07 mg/kg midazolam and 0.1 mg/kg and 0.2 mg/kg diazepam in 12 healthy subjects

	k_{eo} (min^{-1})	$t_{1/2}k_{eo}$ (min)*	E_{max} (%)	EC_{50} (ng/ml)
Midazolam				
0.03 mg/kg				
Mean ± SD	0.165 ± 0.131	4.2†	88.4 ± 11.8	16.1 ± 18.4
%CV	80†	—	13‡	114†
Range	0.051-0.446	1.5-13.6	68.2-99.8	5.72-64.7
0.07 mg/kg				
Mean ± SD	0.267 ± 0.282	2.6§	93.5 ± 14.5	20.9 ± 18.1
%CV	106§	—	16‡	87‖
Range	0.043-0.899	0.8-16.3	56.6-100	3.5-54.2
0.03+ 0.07 mg/kg				
Mean ± SD	0.213 ± 0.216	3.2	90.9 ± 13.2	18.1 ± 17.8
%CV	101	—	14	99
Range	0.043-0.899	0.8-16.3	56.6-100	3.5-64.7
Diazepam				
0.1 mg/kg				
Mean ± SD	0.630 ± 0.508	1.1‡	72.0 ± 17.5	97.6 ± 62.3
%CV	81‡	—	24	64¶
Range	0.193-1.92	0.4-3.6	40.1-100	21.7-216
0.2 mg/kg				
Mean ± SD	0.472 ± 0.355	1.5†	94.1 ± 11.3	132 ± 183
%CV	75†	—	12‡	139§
Range	0.036-1.06	0.6-19.2	65.2-100	0.1-522
0.1 + 0.2 mg/kg				
Mean ± SD	0.555 ± 0.439	1.2	82.6 ± 18.4	116 ± 137
%CV	79	—	22	119
Range	0.036-1.92	0.4-19.2	40.1-100	0.1-522

k_{eo}, Equilibrium rate constant; $t_{1/2}k_{eo}$, plasma–effect site equilibrium half-life; E_{max}, maximum effect; EC_{50}, effect site concentration at which half of E_{max} was reached; %CV, coefficient of variation.
*Harmonic mean; †n = 10; ‡n = 11; §n = 9; ‖n = 7; ¶n = 8.

tency of each drug could then be determined from the high-dose group data by determination of the plasma concentrations at which 50% of the maximum sedation (EC_{50}) was achieved (mean, 21 and 132 ng/ml for midazolam and diazepam, respectively). Although there was variability in the data, the EC_{50} estimates for the lower doses fell within a similar range (mean, 16.1 and 98 ng/ml for midazolam and diazepam, respectively). Based on comparison of mean EC_{50} values, midazolam is approximately 6 times more potent than diazepam. These results are in agreement with previous data reported in two pharmacokinetic-pharmacodynamic studies in which both drugs were compared with use of transformed EEG data as the parameter to assess pharmacodynamic activity.[2,10] In those studies, midazolam showed an intrinsic steady-state potency approximately 5 to 7 times greater than diazepam.

In this study, the DSST rather than EEG was used as a clinical parameter to compare pharmacodynamic findings for midazolam and diazepam. As can be expected with the use of different methods for the assessment of pharmacodynamic activity, the mean values for EC_{50} differed substantially. Using EEG analysis, Buhrer et al.[2] reported mean ± SD values of 152 ± 148 ng/ml for midazolam and 958 ± 200 ng/ml for diazepam. For both drugs, the EC_{50} values were approximately 7 times higher from transformed EEG data than from DSST data.

It is anticipated that DSST may be used as an alternative to EEG data. There are potential benefits to use of either of these methods, although each method also has its drawbacks. The DSST is a well-known psychometric task that is inexpensive to perform and is easy to use in a clinical setting. In contrast, use of EEG data to assess pharmacodynamic activity has not been completely validated, is more costly to generate, and is more difficult to perform. In addition, there has been little agreement on how the EEG data should be handled for pharmacodynamic analysis of sedative hypnotics. However, the use of EEG generates continuous data on sedation and allows for a larger range of measurable effect. The DSST has a much smaller

Table II. Pharmacokinetic parameters after intravenous infusions of 0.03 mg/kg and 0.07 mg/kg midazolam and 0.1 mg/kg and 0.2 mg/kg diazepam in 12 healthy subjects

Parameter	Midazolam		Diazepam	
	*0.03 mg/kg**	*0.07 mg/kg*	*0.1 mg/kg*	*0.2 mg/kg*
C_{max} (μg/ml)				
Mean ± SD	0.28 ± 0.16	0.53 ± 0.33	1.12 ± 0.50	2.39 ± 0.98
%CV	57	62	45	41
Range	0.04-0.50	0.08-1.01	0.45-1.94	0.71-4.30
$t_{1/2}$ (min)				
Mean ± SD	2.0 ± 0.6	3.1 ± 2.0	3.0 ± 0.8	2.7 ± 1.4
%CV	30	64	26	50
Range	1.0-3.0	1.5-8.0	2.0-5.0	1.5-6.0
AUC(0-∞) (μg min/ml)				
Mean ± SD	4.02 ± 1.37	8.80 ± 2.98	33.9 ± 15.4	66.6 ± 9.9
%CV	34	34	45†	15†
Range	0.46-5.67	3.61-13.49	20.2-76.1†	53.0-86.6†
$t_{1/2}$ (min)†				
Mean ± SD	66.6	79.7	§	§
%CV	—	—	—	—
Range	—	31.7-108.0	64.6-105.5	—
CL (ml/min/kg)				
Mean ± SD	12.4 ± 17.7	9.4 ± 4.8	§	§
%CV	143	52	—	—
Range	5.3-65.7	5.2-19.4	—	—
Vd_β (L/kg)				
Mean ± SD	1.0 ± 0.7	1.1 ± 0.6	§	§
%CV	70	51	—	—
Range	0.5-3.0	0.6-2.3	—	—

C_{max}, Maximum plasma concentration; t_{max}, time of C_{max}; AUC(0-∞), area under the concentration-time curve from zero to infinity; $t_{1/2}$, half-life; CL, systemic clearance; Vd_β, apparent volume of distribution; AUC(0-t), area under the concentration-time curve from time zero to the last measurable concentration.
**n* = 11 subjects; †AUC(0-t); ‡harmonic mean; §not obtainable.

pharmacodynamic range and results in larger intersubject variability than the EEG. An additional concern with use of the DSST is that the potential exists for the subject to learn how to perform this task, which could then skew the pharmacodynamic results. This potential does not exist when the EEG method is used. In the current study, to account for a learning curve, subjects performed the DSST in several practice sessions before dosing as a measure of the baseline effect. Overall, the results achieved with use of the DSST method appear to correlate well with those obtained with use of EEG methods.[7]

The $t_{1/2}k_{eo}$ was approximately 2½ times longer for midazolam than for diazepam. Previous data that used EEG data as a pharmacodynamic marker have shown similar results, with the $t_{1/2}k_{eo}$ being about 3 times longer for midazolam than for diazepam (4.8 versus 1.6 minutes).[2]

Midazolam was shown to have a short $t_{1/2}$ (<1½ hours), large Vd_β (~1 L/kg), and a relatively high plasma CL (9 to 12 ml/min/kg). These results are in agreement with previously published data, where mean $t_{1/2}$ values were reported as 1.5 to 2.8 hours (range, 1.2 to 6.5 hours), mean Vd_β as 0.8 to 2.3 L/kg (range, 0.5 to 3.5 L/kg), and mean CL as 5.8 to 11.0 ml/min/kg (range, 5.1 to 16.4 ml/min/kg).[10,11] Extensive intersubject variability was seen in the data from this study; however, this was also present in previously published data. The pharmacokinetics of diazepam could not be assessed because of inadequate duration of blood sampling and therefore are not described here.

Simultaneous modeling of the pharmacokinetic and pharmacodynamics of midazolam relative to diazepam has improved our understanding of the significance of k_{eo} and its contribution to determination of the appropriate dosing of such drugs in a clinical situation. In addition, information on the relative potency of these two agents was clarified with this approach because pharmacokinetic-pharmacodynamic modeling provides a means of ascertaining relative potency with precision.

Incomplete understanding of the pharmacokinetic-pharmacodynamic relationships of midazolam resulted

in an initial dose recommendation that led to considerable overdosage of some patients. This misunderstanding may have occurred because only dose-effect relationships were assessed in early trials, which did not provide information about the importance of the lag-time to effect (k_{eo}) of midazolam with regard to diazepam. The result of this, clinically, was that the interval between multiple doses of midazolam was not long enough. In addition to the differences in lag-time to effect, the difference in potency between midazolam and diazepam were not clearly defined in the early studies. Diazepam was thought to be nearly equipotent with midazolam, again resulting in inappropriate dose recommendations. Later work by Buhrer[2] assessing the concentration-effect relationship, which was confirmed by this study, showed that midazolam has a lag-time to the onset of peak effect, unlike diazepam. In addition, this work clearly showed that midazolam was 5 to 6 times more potent than diazepam. Application of pharmacokinetic-pharmacodynamic modeling would have resulted in the recommendation of a dose regimen that was safe and efficacious.

The pharmacodynamic activities of midazolam and diazepam were compared after two different doses of each drug with use of the DSST as a measure of drug effect. The $t_{1/2}k_{eo}$ was approximately 2½ times longer for midazolam than that for diazepam and, based on the EC_{50}, midazolam had approximately a sixfold greater intrinsic potency than diazepam.

We sincerely thank Mr. Peter Soni for his technical assistance in the compilation of this report.

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