Semilinear Canonical Correlation Applied to the Measurement of the Electroencephalographic Effects of Midazolam and Flumazenil Reversal

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Background: The electroencephalographic (EEG) effect of benzodiazepines, and midazolam in particular, has been described using simple measures such as total power in the beta band, waves vs. in the beta band and total power from aperiodic analysis. All these parameters failed to consistently describe the EEG effect of midazolam in a study in which large doses of midazolam were infused, and the effect subsequently reversed with flumazenil. Using a technique called semilinear correlation it is possible to extract a parameter from the EEG that is statistically optimally correlated with the apparent concentration of the benzodiazepine in the effect site. This method has been used to develop new univariate measures of the effects of opioids on the EEG but has not previously been applied to the EEG effects of benzodiazepines.

Methods: Data from ten subjects who received an infusion of midazolam were analyzed. The data were divided into “learning” and “test” sets. The learning set consisted of ten studies in which the volunteers received an infusion of 2.5 mg/min of midazolam. Semilinear canonical correlation was used to extract an univariate descriptor of the EEG power spectrum. The test set comprised the same subjects on subsequent visits, in which the subjects received a continuous infusion of midazolam to maintain 20% or 80% of the peak drug effect for 3 h. Twenty minutes after start of the midazolam infusion, the patient received an infusion of flumazenil to acutely reverse the benzodiazepine drug effect. The weights obtained from the learning set were tested prospectively in the test set, based on the coefficient of multiple determination, $R^2$, obtained by fitting the EEG effect to a sigmoid $E_{max}$ model.

Results: The canonical univariate parameter of benzodiazepine drug effect on the EEG, when applied to the test set receiving the midazolam infusion with flumazenil reversal, yielded a median $R^2$ of 0.78. The median $R^2$ of six commonly used empirical EEG measures of drug effect ranged from 0.18 to 0.55.

Conclusions: The canonical univariate parameter for benzodiazepine drug effect on the EEG correlates more accurately and consistently with the predicted EEG effects of midazolam and its reversal than previously reported EEG measures of benzodiazepine effect. (Key words: Monitoring; electroencephalographic analysis. Pharmacodynamics, benzodiazepines; flumazenil; midazolam. Statistical method: semilinear canonical correlation.)

THE electroencephalogram (EEG) can be used to characterize the relationship between drug concentration in the plasma and drug effect. Midazolam increases the activity in the beta frequency range (13–30 Hz) of the EEG and decreases the activity in the alpha range (8–12 Hz). Several investigators have described univariate measures of the EEG effects of benzodiazepines. Greenblatt et al. used the percentage of total EEG amplitude in the 13–30-Hz range as a measure of midazolam and diazepam effect. Breimer et al. used the total number of waves per second in the 12–30-Hz range, as calculated using aperiodic analysis, as a measure of midazolam effect on the EEG. Bührer et al. systematically explored different parameters of the EEG that could be used in describing the benzodiazepine-induced changes in the EEG. Bührer concluded that the total voltage from aperiodic analysis directly reflected the most prominent drug-induced change seen in the raw EEG.

In a previous study of flumazenil pharmacodynamics, we used the EEG to measure the effect of midazolam and its acute reversal with flumazenil on the central
nervous system over time. In our first analysis of these data, we observed that previously reported measures of benzodiazepine drug effect were generally inadequate in describing the effect of midazolam and its reversal on the EEG. Therefore, we sought a new measure of the effect of midazolam and its reversal on the EEG.

Using a statistical method called semilinear canonical correlation (SCC), Gregg et al. developed a consistent measure of the effects of opioids on the EEG. In this investigation, we used SCC to characterize the effects of benzodiazepines on the EEG. Two benzodiazepine effects were examined: the effect of midazolam on the EEG, and the effect of flumazenil on the EEG when administered during a steady-state infusion of midazolam. Using SCC, we developed a measure of benzodiazepine effect on the EEG. We then examined the difference between this new measure and previously reported measures in correlating with midazolam and flumazenil effect-site concentration.

Methods

Data

The data set used for this investigation came from a study designed to determine the pharmacodynamics of flumazenil in the presence of midazolam. The study was designed so that each volunteer participated in three sessions. After Institutional Review Board approval and informed consent were obtained, ten healthy volunteers, aged 21–43 yr, weighing 72–88 kg, were enrolled in the study. A radial artery catheter for blood sampling and two intravenous catheters were inserted. Monitoring consisted of a 3-lead electrocardiogram and a pulse oximeter. Ventilation was either spontaneous or assisted as required to maintain normocarbia, as determined by regular arterial blood gas measurements.

The study design for each session follows. Session 1. Midazolam was infused at a constant rate of 2.5 mg·min⁻¹ until a maximum increase of EEG power was obtained as determined by the on-line EEG waveform analysis. The total dose ranged from 27.6 to 30 mg. Arterial blood samples were drawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4.5, 6, 8, 10, and 12 min during and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 4.5, 6, 8, 10, 15, 20, 30, 60, 90, 120, 150, and 180 min after the infusion, and venous blood samples were drawn at 240, 300, 360, 420, and 480 min after the infusion. The pharmacokinetics of midazolam were determined for each individual using extended least-squares nonlinear regression. The equilibration rate between plasma and effect site, kᵩ, was determined nonparametrically. The measure of drug effect was the total voltage·s⁻¹, as measured using aperiodic EEG analysis. Ten persons completed session 1.

Session 2. In the second study session, separated from the first by at least 2 weeks, the volunteer received a computer-controlled infusion of midazolam to maintain 20% of the maximal EEG effect for 200 min. The pharmacokinetics used by the computer-controlled infusion pump were those determined for each individual in session 1, and the targeted concentration was the effect-site concentration that produced 20% of maximum EEG effect, again as determined for the volunteer in study session 1. After maintaining a constant plasma midazolam concentration for 20 min, flumazenil was infused at a rate of 0.5 mg·min⁻¹ until the EEG effect of midazolam was reversed completely. Complete reversal was defined as a return to baseline EEG total power. When the EEG signal was not reliable, the reversal from midazolam sedation was assessed clinically. The computer-controlled infusion pump continued to maintain a constant midazolam concentration during and after the flumazenil infusion. The infusion scheme is outlined in figure 1. Arterial flumazenil concentrations were measured at 0.5, 1, 1.5, 2, 2.5, 3, 4, 4.5, 6, 7, 8, 9, and 10 min during and at 0.5, 1, 2, 3, 4, 4.5, 6, 8, 10, 15, 20, 30, 40, 60, 90, 120, 150, 180, and 240 min after the flumazenil infusion, and venous flumazenil concentration was measured at 300, 360, 420, and 480 min after the flumazenil infusion. The parameters of a three-compartment mamilary model were fitted to the measured flumazenil concentration data using extended least squares. Six persons completed session 2. Of the four participants who completed study 1 but not study 2, one was not invited back for subsequent studies because of a combative response to midazolam, and the other three elected not to participate in subsequent studies.

Session 3. Session 3 was identical to session 2 except that the target midazolam concentration was the effect-site concentration associated with 80% of the maximum EEG effect, again as determined from study 1. As de-
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**Fig. 1.** Infusion scheme of the three study sessions. Session 1 with the midazolam infusion represented by the thick line (*top*). The middle and the lower panels show the time course of the midazolam and of the flumazenil infusions (*middle and bottom*). The midazolam computer-controlled infusion pump starts at -20 min and the flumazenil at time zero. The difference between sessions 2 and 3 is the target concentration for midazolam.

Electroencephalographic Analysis

The EEG was acquired and amplified by an electroencephalograph (EEG-5210, Nihon Kohden, Irvine, CA) using a high-frequency filter at 70 Hz and with a time constant of 0.3 s. It was digitized at 128 samples/s and saved to hard disk. The raw signal was analyzed using Fourier transformation and aperiodic analysis.

Fourier transformation of 2 s epochs yielded a power spectrum 0–64 Hz in frequency bins of 0.5 Hz. The phase data from the Fourier transformation were discarded. The power at 0 Hz, reflecting the average height of the signal, and the power above 30 Hz were discarded.

No smoothing of the frequency spectrum within an individual epoch was applied. The power in each frequency bin was averaged over 20 s (10 epochs). From the spectral analysis, we calculated the total power and power in the beta band (15–30 Hz) as suggested by Greenblatt.

Aperiodic analysis determined the frequency and amplitudes of the EEG on a wave-by-wave basis over 20 s epochs. The aperiodic analysis was performed as described by Gregory and Pettus and implemented by the authors in the C programming language. From the aperiodic analysis, we calculated the amplitude per second, as suggested by Bührer, and and the number of waves per second, as suggested by Breimer.

In a previous study, we found that none of the previously described EEG measures of benzodiazepine drug effect consistently characterized the reversal of midazolam drug effect with flumazenil. To develop a new measure of the effect of benzodiazepines on the EEG, we divided these data into a learning set (session 1: midazolam infusion) and a test set (sessions 2 and 3: flumazenil infusion during a steady-state midazolam infusion). The data from the learning set were used to identify a new EEG measure of benzodiazepine drug effect: the canonical univariate parameter for benzodiazepines, (CUPb). The data from the test set subsequently were used to evaluate the CUPb by examining whether it correlated with flumazenil effect-site concentration better than the previously described EEG measures.

The derivation of the CUPb is described in the Appendix. Briefly, after Fourier transformation of the EEG, the EEG spectrum is coalesced into 10 bands of 3 Hz each (0.5–3 Hz, 3.5–6 Hz, and so forth). Then the log of the power in each band is calculated. The canonical univariate parameter for benzodiazepine effect on the EEG is defined as the log power in each of these bands.

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# The Excel spreadsheet used to compute the CUPb is available via the WWW at http://pkpd.icon.palo-alto.medic.va.gov and by ftp to pkpd.icon.palo-alto.medic.va.gov/utility.dir/excel.dir/cupb.xls.

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times a coefficient. So, at time t, the canonical univariate parameter is:

\[
\text{CUP}_B(t) = \text{Coefficient 1 times log power from 0.5 to 3 Hz at time t + Coefficient 2 times log power from 3.5 to 6 Hz at time t + Coefficient 3 times log power from 6.5 to 9 Hz at time t + and so on to Coefficient 10 times log power from 27.5 to 30 Hz at time t.}
\]

The method describes how the SCC technique is used to estimate the terms coefficient 1, coefficient 2, and so on through coefficient 10. The coefficients estimated using SCC are “optimal” in that they represent the coefficients that, within the range of possible solutions, give the best correlation with the predicted effect-site benzodiazepine concentration. A more formal description of the derivation of the CUPB can be found in the Appendix.

**Test Set Application of New Parameters and Comparison.** The test set consisted of the EEG from the subjects during sessions 2 and 3. No subject’s data were excluded from the test set. Although the CUPB was developed as a measure of midazolam drug effect on the EEG, it was tested as a measure of flumazenil drug effect. In other words, the CUPB was tested as a measure of the reversal of midazolam effect.

**Pharmacodynamic Model**

Flumazenil has no intrinsic activity on the EEG. Midazolam-induced changes in the EEG can be reversed by flumazenil.\(^{11,12}\) Thus, a constant midazolam drug effect on the EEG can be viewed as a “baseline EEG” with respect to flumazenil. Changes in the EEG from this baseline during a steady-state midazolam infusion can be attributed to flumazenil. For the pharmacodynamic modeling of the test, set the EEG waveform at 10 min before flumazenil administration until 120 min after flumazenil administration was analyzed. This approach enabled modeling of the pharmacodynamics of flumazenil relative to the steady-state midazolam “baseline EEG” without requiring a model of midazolam—flumazenil interaction.

The relationship between the biophase concentration and the drug effect was modeled as described by equation 3, where now:

\[
t = \text{time. Electroencephalographic effect measures were obtained every 20 s, and } t = 0 \text{ corresponds to the start of the flumazenil infusion. Thus } t \text{ takes on the values } -10 \text{ (10 min after the start of the midazolam infusion), } -9.66\ldots -0.33\ldots 0.33\ldots \text{ until the end of data collection.}
\]

\[
E(t) = \text{EEG effect measured at time } t. \text{ The EEG effects studied are described later.}
\]

\[
E_0 = \text{“baseline” flumazenil effect, } t.e., \text{ the constant effect maintained by the ongoing midazolam infusion.}
\]

\[
E_{\text{max}} = \text{maximal flumazenil effect. In theory, because flumazenil reverses the effect of midazolam, } E_{\text{max}} \text{ equals the effect in a subject free of midazolam and flumazenil.}
\]

\[
I_{C_50} = \text{Steady-state flumazenil concentration that produces a 50% reversal of midazolam effect.}
\]

\[
\alpha = \text{Determines the slope in the linear part of the Hill equation.}
\]

\[
\epsilon = \text{random error.}
\]

Using nonlinear regression, the parameters \(E_0, E_{\text{max}}, I_{C_50}, \alpha, \text{ and } k_{s0} \text{ (which determines } Ce) \text{ were estimated. The correlation } (R^2) \text{ between the estimated measure of benzodiazepine drug effect and the drug effect measured using the population value of CUPB estimated from the learning set was calculated for each person. This correlation was compared with the correlation obtained with several other measures of benzodiazepine drug effect on the EEG as described earlier.}

**Results**

**Learning Set**

Three sets of SCC coefficients were derived from the learning sample. They are depicted in figure 2 and listed in table 1. The first is computed using the pooled approach. The other two sets are the median and the average values computed from the individual SCC parameter sets. The three sets of coefficients produced nearly identical \(R^2\) values in the test set. However the mean of the \(R^2\) values obtained with the pooled approach was the greatest in the learning set. Thus, we compared the empirically derived measures of benzodiazepine EEG effect to the CUPB characterized using the pooled-data analysis.

Using total voltage from aperiodic analysis, we calculated a \(T^{1/2} k_{s0}\) of 2.4 min (range 0.7–4.3 min) for
midazolam. Using the CUP_b, we calculated a T½ k_e0 of 2.9 min (range 0.5–6.0 min). The concentration that results in 50% of maximal effect (IC50) was 348 ng·ml⁻¹ calculated with the data from the aperiodic analysis and 242 ng·ml⁻¹ with the SCC parameters. In the learning set, the estimates of T½ k_e0 and IC50 based on CUP_b are not significantly different than those based on total voltage from aperiodic analysis (P > 0.05).

Test Set
Pharmacodynamic Analysis No data were excluded from the pharmacodynamic analysis, but some parameter estimates were excluded from the summary tables and figures and from the calculation of the median, according to the following criteria:

1. Visual inspection of the EEG measure over time had to show some evidence of drug effect after flumazenil administration.
2. The estimate of T½ k_e0 had to be within the range of 30 s to 60 min. Values outside this range could not reasonably be supported by our study design.
3. The IC50 had to be less than 100 ng/ml. Values larger than this usually indicated failure of the model or study design to identify E_max.
4. The slope factor in the Hill equation had to be smaller than 10. At slope factors above 10, the Hill equation resembles a step function.

Based on these criteria, using the CUP_b as a measurement of benzodiazepine effect on the EEG required exclusion of none of the T½ k_e0 estimates (fig. 3), four of the estimates of IC50 (fig. 4), and two of the estimates of the slope factor (fig. 5). Every empirical measure of benzodiazepine effect on the EEG required exclusion of more individual estimates than were required by the CUP_b.

The T½ k_e0 for flumazenil, calculated using the CUP_b, was 2.4 min (ranging from 0.3 to 5.1 min). The IC50 for flumazenil calculated using the CUP_b was 30 ng·ml⁻¹ (ranging from 9 to 73 ng·ml⁻¹ and the slope factor was 1.3 (ranging from 0.4 to 3.6). Figures 3, 4, and 5 show the estimates of k_e0, IC50, and the slope factor for the CUP_b, and the empirical measures of benzodi-
SCC APPLIED TO THE EEG EFFECT OF BENZODIAZEPINES

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<th>Parameter</th>
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Fig. 4. The distribution of the half-time IC₅₀ for flumazenil calculated from the test set. Unreasonably large values corresponding to step function rather sigmoidal relationships between effect-site concentration and the electroencephalographic component, are not plotted or included in the calculation of the median.

azepine EEG effect. Although more estimates are shown for the CUP₀ than for the other parameters because fewer estimates were rejected as outliers, in general there is less scatter among the estimates of kₑ₀, IC₅₀, and the slope factor using the CUP₀ as the measure of benzodiazepine drug effect than using the empirical measures of benzodiazepine drug effect.

Comparative Performance of Derived Semilinear Canonical Correlation Parameters All data in the test set were included in the comparison of the performance among the different EEG measures of benzodiazepine drug effect. The R² values and their medians are given in figure 6. For each subject, the R² value in individual subjects are connected with a dashed line among the different measurements of drug effect. Occasionally, a patient showed good correlation between flumazenil effect-site concentration and EEG effect, however, the highest correlations were those obtained using the CUP₀ as the measure of benzodiazepine EEG effect. The median R² value obtained with the CUP₀ was 0.78 ranging from 0.51 to 0.87. The second best R² values were obtained using the power in the beta band as the measure of benzodiazepine EEG effect. For this measurement, the median value of R² was 0.56, ranging from 0.12 to 0.71. Note that the median value of R² using power in the beta band is nearly identical with the worst performance with the CUP₀.

Low R² values were observed in those cases where there was very little visible effect of flumazenil on the EEG. Figure 7 shows a subject with no observable effect (top) with the empirical measure (total voltage · s⁻¹ from aperiodic analysis) and the EEG effect over time calculated using the CUP₀. The CUP₀ distilled from the EEG waveform demonstrates an effect whose magnitude and time course match the expected time course of flumazenil effect-site concentration.

Discussion

The EEG is a continuous and sensitive measure of drug effect on the central nervous system. This makes it a useful pharmacodynamic measure of drug effect for centrally acting drugs. The EEG response is not synonymous with anesthesia, but it is at least a measure of drug effect in the target organ. An ideal pharmacodynamic measurement should be consistent for drugs within the same class and insensitive to noise. Although measures of anesthetic drug effect such as spectral edge 95% or median frequency have been useful in defining the pharmacodynamics of opioids, barbiturates, and inhaled anesthetics, in a prior study we demonstrated that using SCC it was possible to identify an EEG measure of opioid effect that was more consistent than these previously defined measures.

The choice of an empirical EEG effect measure for opioids is easier than for benzodiazepines because of the unambiguous EEG changes caused by opioids: in-

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increased amplitude and decreased frequency. The response of the EEG to increasing concentrations of benzodiazepines is more complex. Benzodiazepines initially increase the power in the beta and delta bands. As the benzodiazepine concentration increases, an increase of delta activity is observed. Finally, the beta activity diminishes once the subject loses consciousness. However, because the benzodiazepines themselves induce sleep, it is not possible to maintain wakefulness when given large doses of benzodiazepines.

The data in the current study were gathered to examine the pharmacodynamics of flumazenil. The empirical measures of EEG drug effect provided an acceptable description of the time course of the drug effect during session 1, the midazolam infusion. However, we were unable to find an empirical measure of benzodiazepine EEG effect that worked in all subjects in sessions 2 and 3, in which the EEG effects of midazolam were acutely reversed by flumazenil. This suggests that the previously described empirical measures of benzodiazepine effect are neither consistent nor accurate measures of the EEG response to benzodiazepines.

The canonical univariate parameter of benzodiazepine drug effect, CUP\textsubscript{B}, demonstrated an improvement in correlation with effect-site benzodiazepine concentration. The pooled approach to obtaining EEG components was preferred in this study because it provided the best correlation in the learning set. The CUP\textsubscript{B} calculated using a pooled analysis also proved consistent in the test set. Not shown in our results is the performance of the average and median CUP\textsubscript{B}, both of which performed as well in the test set as the CUP\textsubscript{B} derived from the pooled analysis.

Some of the of IC\textsubscript{50} values, of the T\textsuperscript{1/2}ke0 values and of the slope factor values, were excluded from the final analysis. Unfortunately, the sigmoidal relationship has a degenerate solution when \( F_{\text{max}} \) cannot be estimated from the data and is not known \textit{a priori}. In this case, the sigmoidal \( F_{\text{max}} \) relationship becomes a linear equation with an intercept of \( E_0 \) and a slope of \( E_{\text{max}}/IC_{50} \). In this situation, because the value of \( E_{\text{max}} \) is arbitrarily large, the value of IC\textsubscript{50} is also arbitrarily large. That fewer persons had this problem with the CUP\textsubscript{B} than with other measures of EEG effect is further indication of the usefulness of the parameter. It is noteworthy that this is not a problem with CUP\textsubscript{B} itself, but rather a problem with identifiability of the individual parameters of the pharmacodynamic model. No participants

![Graph](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAADAAAAB7CAYAAABf3LcDAAAABGdBTUEAALGPC/xhBQAAAgAElEQVR42u3XQsEQ...</raw_text
were excluded from the R² analysis, which is the portion of the manuscript that tests the performance of the CUP₉ itself. The IC₅₀ and Hill equation results measures the CUP₉ as a tool for estimating pharmacodynamic parameters. In those cases where the dynamic range explored was insufficient to accurately estimate all of the parameters, this does not represent a failure of the CUP₉.

The poor performance of previously defined measures of benzodiazepine EEG effect contrasts with the reports of other investigators. Mandema et al.\(^{14,15}\) used the average amplitude in the 11.5-30 Hz frequency band for pharmacokinetic/pharmacodynamic modeling of the midazolam/flumazenil interaction in a study with rats. Rats have a fundamentally different response to benzodiazepines, in that they can be kept awake after receiving high doses of midazolam. Thus, the confounding EEG changes seen when a human loses consciousness with high doses of midazolam are not observed in rat studies. We cannot readily explain why the number of waves was not a consistently useful measure of benzodiazepine effect in this study, given the good results with this parameter reported by Breimer et al.\(^{5}\) In the previous human studies, only the effects of benzodiazepine agonists were tested. It may be that this setting is less demanding of the chosen EEG measure than one in a study involving the acute reversal of benzodiazepine effect. Additionally, the other measures tend to focus on just a single frequency range within the EEG, whereas the SCC approach uses the information in all frequency bands. It may be the case that there is information in the full EEG spectrum that does not improve the measurement of benzodiazepine agonist response, but that is crucial to measuring the EEG effects of benzodiazepines when combined with antagonists. As noted previously, the data were not gathered.

As noted previously, these data were not originally gathered to define a new EEG measure of benzodiazepine drug effect. However, the availability of data reflecting both the EEG effects of midazolam and its reversal by flumazenil provided an opportunity to refine the measurement of benzodiazepine drug effect. In future studies, we intend to examine the behavior of the CUP₉ for a spectrum of benzodiazepines, just as Gambus did for opioids.

To conclude, we have used SCC to identify a new measure of benzodiazepine drug effect on the EEG. This new measure, the "canonical univariate parameter" or CUP₉, proved in a test set to be considerably more accurate and consistent than previously defined measures of benzodiazepine drug effect. The CUP₉ described the EEG effect of benzodiazepines in a setting where midazolam drug effect was acutely reversed by an infusion of flumazenil. The canonical univariate parameter may be a useful new tool for studying the pharmacodynamics of benzodiazepines using the EEG as a measure of drug effect.

Appendix: Derivation of the Canonical Univariate Parameter for Midazolam from the Learning Set

**Pharmacodynamic Model**

A four-compartment, the effect site, connected to the central compartment of the kinetic model (fig. A1) was used to describe the time delay between concentration in the blood and the biophase. By definition, the effect site has no influence on the time course of the plasma concentration. The elimination from this compartment is defined by a rate constant denoted with \( k_{e_i} \). This constant also is called the plasma effect-site equilibration rate constant because it describes the time for 50% equilibration between the effect site and a constant plasma concentration (as might be achieved with a computer-controlled infusion pump). The model for effect-site concentration is defined by equations:

\[
\begin{align*}
Cp(t) &= \sum_{i=1}^{3} A_i e^{-\lambda_i t} I \\
Ce(t) &= Cp(t) * k_{e_i} e^{-k_{e_i} t}
\end{align*}
\]

where \( Cp \) is plasma concentration, \( A_i \) and \( \lambda_i \) are parameters of the kinetic model, \( Ce \) is effect-site concentration, \( t \) is time, \( I \) is infusion, and \( '*' \) represents the convolution operator. The \( Cp(t) \) in [1.2] was calculated for each subject with the individual parameters. The phar-

![Fig. A1. Effect-site model. The kinetic model consisted of a three-compartment model with the compartments with volumes V₁, V₂, V₃, and clearances C₁₁, C₁₂, and C₁₃. By adding an effect compartment (E), which is connected with the central compartment through a rate constant \( k_{e_i} \), which has an elimination rate constant of \( k_{e_i} \), the equilibration delay between central compartment and effect compartment is described by \( k_{e_i} \).](image_url)
macodynamic model defines the relation between the effect site concentration and the effect. A sigmoid $E_{\text{max}}$ model (Hill equation) was used:

$$E(t) = I_{0} + (E_{\text{max}} - I_{0}) \frac{C(t)^{\alpha}}{IC_{50}^{\alpha} + C(t)^{\alpha}} + e$$

Where:
- $t$ = time.
- Electroencephalographic effect measures were obtained every 20 s, and $t = 0$ corresponds to the start of the midazolam infusion.
- $E(t)$ = EEG effect measured at time $t$.
- $E_{\text{max}}$ = maximal midazolam effect.
- $I_{0}$ = baseline EEG effect when no drug is infused.
- $IC_{50}$ = Steady-state midazolam concentration that produces an effect halfway between $E_{0}$ and $E_{\text{max}}$.
- $\alpha$ = Determines the slope in the linear part of the Hill equation.
- $e$ = random error.
- $E(t)$ is an arbitrary function of the digitized EEG. This function is of fixed, defined form for the previously used measures such as total power, number of waves in the beta band, and others. With SCC, this function can be a univariate parameter for benzodiazepines, CUP$_{k}$. As defined below, CUP$_{k}$ is to produce an EEG measure of drug effect that ‘optimally’ correlates with effect-site drug concentration.

**Semilinear Canonical Correlation**

Standard linear regression relates a dependent variable to a linear combination or weighted sum of independent variables, plus random error ($Y = w_{1}X_{1} + w_{2}X_{2} + \ldots + w_{n}X_{n} + e$). To minimize the difference between the dependent variable, $Y$, and the prediction, the weights ($w_{i}$) on the independent variables ($X_{i}$) are iteratively searched by some objective criterion (e.g., minimum squared error, maximum likelihood, etc.). If the independent variable also is expressed as a linear combination of individual measures, $Y_{i}$ and coefficients, $\gamma_{i}$ ($\gamma_{i}Y_{i} + \gamma_{i}Y_{i} + \ldots + \gamma_{n}Y_{n}$), the difference between $Y = \gamma_{1}Y_{1} + \gamma_{2}Y_{2} + \ldots + \gamma_{n}Y_{n}$ and $X = w_{1}X_{1} + w_{2}X_{2} + \ldots + w_{n}X_{n}$ can be measured by the correlation between $Y$ and $X$ and this correlation can be used as the objective criterion to be searched to find $\gamma_{1}, \gamma_{2}, \ldots, \gamma_{n}$ and $w_{1}, w_{2}, \ldots, w_{n}$. This approach is standard canonical correlation. In SCC, the left side of the equation, $\gamma_{1}Y_{1} + \gamma_{2}Y_{2} + \ldots + \gamma_{n}Y_{n}$ remains a linear combination of individual measures of the dependent variable and associated coefficients, but the right side becomes a nonlinear function, in this case being the sigmoid-$E_{\text{max}}$ model relating effect-site concentration to drug effect. Semilinear canonical correlation estimates the coefficients, $\gamma_{1}, \gamma_{2}, \ldots, \gamma_{n}$, on the individual measures of the dependent variable, and concurrently estimates the parameters of the nonlinear function. For mathematical tractability, we have limited the number of bins ($n$) to 10. The measure of drug effect at time $t$ (the canonical univariate parameter for benzodiazepines at time $t$, CUP$_{k}(t)$) is thus the linear combination of the coefficients $\gamma_{1}, \gamma_{2}, \ldots, \gamma_{10}$ with the measures of drug effect at time $t$, $Y_{1}(t), \ldots, Y_{10}(t)$.

CUP$_{k}(t) = \gamma_{1}Y_{1} + \gamma_{10}Y_{10}(t)$$

where $n = \text{maximum number of bins} = 10$ in the current case, $Y_{1} = \text{log (power from 0.5 to 3 Hz)}(t), \ldots, Y_{10} = \text{log (power from 29.5 to 30 Hz)}(t)$, $\gamma_{1}$ is the first coefficient, and $\gamma_{10}$ is the coefficient for the 10th bin.

The coefficients $\gamma_{1}, \ldots, \gamma_{10}$ are not known for the benzodiazepines. We estimated these coefficients from the learning set (session 1: midazolam infusion). Eight of ten subjects were included in the analysis.

The reasons to exclude two subjects were as follows: one subject received a multiple infusion scheme that could not be handled by the program we used for the individual estimation of the SCC parameters; and one subject had a paradoxically agitated reaction to midazolam and was not further studied, because we were concerned that our estimate of the coefficients from the learning set would be degraded by inclusion of the very noisy data from this person. Note that no EEG waveforms were excluded from the test set as described later, where the performance of the CUP$_{k}$ was measured.

The model [1.3] is fitted separately to each individual with $E(t)$ replaced by $\gamma_{1}\log p_{1} + \ldots + \gamma_{10}\log p_{10}$ where $p_{i}$ is the power in the i-th frequency range. Specifically, the EEG from 0.5 to 30 Hz is divided into ten "bins" containing the power as calculated by Fourier transformation. Thus, $p_{1}, p_{2}, \ldots, p_{10}$ denote the powers in the 0.5–3 Hz, 3–5 Hz, 5–6 Hz, ..., 27.5–30 Hz frequency ranges. The objective criterion to be minimized, the coefficient of determination, is defined as:

$$R^{2} = 1 - \frac{\text{SSE}}{\text{SSTO}}$$

where

$$\text{SSTO} = \sum_{i=1}^{n} (Y_{i} - \bar{Y})^{2}$$

$$\text{SSE} = \sum_{i=1}^{n} (Y_{i} - \hat{Y}_{i})^{2}$$

Thus, we obtain $\gamma_{1}, \ldots, \gamma_{10}$, the ten coefficients for subject $i$, where $i = 1, \ldots, 8$. (number of subjects in the learning sample from which the SCC parameters have to be derived). This develops a CUP$_{k}$ for each individual. As observed by Gregg et al.,6 there is no necessarily correct method to combine estimates of the CUP$_{k}$ in individuals to generate an optimal CUP$_{k}$ for a population. We investigated three methods to combine the individual estimates of CUP$_{k}$. The first was to simply average the corresponding coefficients over the eight subjects:

$$\bar{\gamma}_{j} = \frac{1}{8} \sum_{i=1}^{8} \gamma_{j}(i), \ j = 1, \ldots, 10.$$ (7)

This is the approach chosen by Gregg and colleagues.4 The second approach was to define the optimal value of each coefficient as the median over the eight subjects:

$$\gamma_{j} = \text{median}(\gamma_{j}(1), \ldots, \gamma_{j}(8)), \ j = 1, \ldots, 10.$$ (8)

These two methods are "two-stage" methods in that we first obtain individual estimates $\gamma_{j}(i), i = 1, \ldots, 8$, and then calculate the optimum parameter as the mean or median of the estimates in each individual. The third approach was to pool the data for all eight subjects and use SCC to calculate a single estimate of the coefficients. Let $P_{10}(t), \ldots, P_{10}(t)$ denote the powers in the 10 frequency bands measured at time $t$ for the ith subject, and let

$$E_{10}(t) = \gamma_{1}\log P_{10}(t) + \ldots + \gamma_{10}\log P_{10}(t)$$

where $n = \text{maximum number of bins} = 10$ in the current case, $Y_{1} = \text{log (power from 0.5 to 3 Hz)}(t), \ldots, Y_{10} = \text{log (power from 29.5 to 30 Hz)}(t)$, $\gamma_{1}$ is the first coefficient, and $\gamma_{10}$ is the coefficient for the 10th bin.

The coefficients $\gamma_{1}, \ldots, \gamma_{10}$ are not subject specific, but apply to all individuals. Let

$$E_{10}(t) = E_{10}(t) + (E_{\text{max}}(t) - E_{10}(t))$$

the sigmoid $E_{\text{max}}$ model. Observe that the ith individual has his own values of the parameters $E_{10}(t), E_{\text{max}}(t), IC_{50}$, $\alpha(0), k(0)$ (which de-
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terms Ce(t). Our pooled approach is to estimate γ1, . . . , γ10 and 
E(t), Emax, IC50, α, and ke(0) for i = 1, . . . , 8 by the values that minimize

\[ \sum_{i=1}^{8} \sum_{j=1}^{N} \left[ E^{(i)}(t) - E^{(0)}(t) \right]^2, \]

subject to the constraint

\[ \frac{1}{N} \sum_{i=1}^{8} \sum_{j=1}^{N} \left[ E^{(i)}(t) - \bar{E} \right]^2 = 1, \]

where N is the total number of observations in the eight subjects and

\[ \bar{E} = \frac{1}{N} \sum_{i=1}^{8} \sum_{j=1}^{N} E^{(i)}(t). \]

Symbols

- \( \gamma_i \) Coefficients defining the CUP
- \( \bar{\gamma} \) Median of the coefficients \( \gamma_1, \ldots, \gamma_{10} \)
- \( \bar{\gamma} \) Average of the coefficients \( \gamma_1, \ldots, \gamma_{10} \)
- \( \bar{Y} \) Mean of observed effect
- \( \bar{\bar{Y}} \) Predicted effect
- \( \bar{Y} \) Observed effect
- \( \lambda(0) \) Macro rate constant in the kinetic model
- \( \alpha \) Shape parameter in the Hill equation
- \( C(t) \) Effect site concentration at time t
- \( C_p(t) \) Plasma concentration at time t
- \( C_{UP} \) Canonical univariate parameter for the benzodiazepines
- \( e \) Additive error in the pharmacodynamic model
- \( E^{(i)}(t) \) Electroencephalographic effect at time t calculated for subject i using the population coefficients as the weights to the log power in the frequency bins
- \( E_0 \) Electroencephalographic baseline effect, when no drug is present
- \( EEG \) Electroencephalogram
- \( E_{max} \) Maximum possible effect caused by the drug
- \( IC_{50} \) Effect site concentration resulting in an effect equal to (\( E_0 + E_{\max} \))/2
- \( k_e \) Rate constant for drug transfer from plasma to the effect site
- \( P(t) \) The power in the frequency bands 1 . . . , 10 at time t for ith individual
- \( R^2 \) Coefficient of multiple determination, (1 − SSE)/SSTO
- SCC Semilunar canonical correlation
- SSE Sum of squared errors from estimating the effect by the pharmacodynamic model
- SSTO Sum of the squared total deviation of measured effect from its mean

References