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Validation of the Alfentanil Canonical Univariate Parameter as a Measure of Opioid Effect on the Electroencephalogram

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Background: **Several parameters derived from the multivariate electroencephalographic (EEG) signal have been used to characterize the effects of opioids on the central nervous system. These parameters were formulated on an empirical basis. A new statistical method, semilinear canonical correlation, has been used to construct a new EEG parameter (a certain combination of the powers in the EEG power spectrum) that correlates maximally with the concentration of alfentanil at the effect site. To date, this new canonical univariate parameter (CUP) has been tested only in a small sample of subjects receiving alfentanil.**

Methods: **The CUP was tested on EEG data from prior studies of the effect of five opioids: alfentanil (n = 5), fentanyl (n = 15), sufentanil (n = 11), trefentanil (n = 5), and remifentanil (n = 8). We compared the CUP to the commonly used EEG parameter spectral edge, $SE_{95\%}$. The comparison was based on the signal to noise ratio, obtained by fitting a nonlinear pharmacodynamic model to both parameters. The pharmacodynamic parameter estimates obtained using both measurements were also compared.**

Results: **The values for signal-to-noise ratio were significantly greater for the CUP than for $SE_{95\%}$ when considering all the opioids at once. The pharmacodynamic estimates were similar between the two EEG parameters and with previously published results. Semilinear canonical correlation coefficients estimated within each drug group showed patterns similar to each other and to the coefficients in the CUP, but different from coefficients for propofol and midazolam.**

Conclusions: **Although the CUP was originally designed and tested using alfentanil, we have proven it to be a general measure of opioid effect on the EEG. (Key words: Analgesics: opioids. Electroencephalogram: canonical univariate parameter; spectral edge. Statistical modeling: semilinear canonical correlation.)**

THE electroencephalogram (EEG) has been widely used as a measure of anesthetic drug effect on the central nervous system (CNS). It is a continuous, noninvasive measure from which estimates can be made about the time course of anesthetic drug concentration within the CNS. Additionally, the EEG has proven to be a useful measure of drug potency[1] and, as such, has played an important role in the development of new anesthetic drugs.[2,§]

Electroencephalographic measures of opioid drug effect reflect both the time course and relative potency of opioid drug effect on the cerebral cortex, as reviewed by Shafer and Varvel.[3] This is not surprising, because the EEG response to opioids is clearly a function of the plasma concentration[4,5] (after compensating for diffusion delay to the effect site), and the clinical response to opioids is also a function of the plasma concentration, as demonstrated by Ausems *et al.*[6]

Since the early work of Bickford describing the effects of central acting drugs using the EEG,[7] many different methods of analyzing the EEG signal have been used to relate the EEG effect to drug concentration. Spectral edge, total power, power in the δ, α, θ, and β frequencies, median frequency, total number of waves per second, autocorrelation, and a variety of ratios of different

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§ Hermann DJ, Muir KT, Egan TD, Stanski DR, Shafer SL: Use of pharmacokinetic-pharmacodynamic modeling for developing rational dosing strategies for Phase III Clinical Trials: Remifentanil. Second International Symposium on Measurements and Kinetics of In Vivo Drug Effects, Noordwijkerhout, April 1994.

Table 1. Description of the Main Characteristics of the Five Original Studies on Which We Based Our EEG Analysis.

	No. of Individuals	Rate	EEG End Point	Goal of the Study	Reference
Fentanyl	10	150 μg/min	δ waves (max effect)	Age effect on PK/PD	4
Fentanyl	5	2.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	δ waves (max effect)	Trefentanil control	2
Alfentanil	5	22 $\mu g \cdot kg^{-1} \cdot min^{-1}$	δ waves (max effect)	Trefentanil control	2
Sufentanil	11	18.75 μg/min	δ waves (max effect)	Potency relative to fentanyl	5
Trefentanil	5	22 $\mu g \cdot kg^{-1} \cdot min^{-1}$	δ waves (max effect)	Crossover design with alfentanil and fentanyl	2
Remifentanil	8	1–8 $\mu g \cdot kg^{-1} \cdot min^{-1}$	None	Dose ranging	9

EEG = electroencephalogram; max = maximum; PK/PD = pharmacokinetics and pharmacodynamics.

frequency bands are all examples of EEG processing techniques that have been applied in an effort to reduce the complex EEG waveform to a single (*i.e.*, univariate) measure of the effect of anesthetic drugs on the EEG. These parameters were developed to quantitate some aspect of the EEG that could be seen by visual inspection to change after drug administration. Thus, the selection of EEG parameters has been mostly empirical, in that the EEG signal processing algorithms have been chosen in an *ad hoc* manner. An alternative is to use an appropriate statistical method to define the EEG parameter that "optimally" correlates with anesthetic drug concentration at the site of drug effect.

One such method is semilinear canonical correlation (SCC). Semilinear canonical correlation is a statistical technique that can be used to characterize the particular combination of EEG frequencies that optimally correlates with effect site opioid concentration. Semilinear canonical correlation searches for the best linear combination of the powers in the frequency spectrum of the EEG, while rearranging and estimating the pharmacodynamic parameters in an iterative fashion, trying to obtain the combination of both EEG measure and pharmacodynamic parameter estimates that maximizes the signal-to-noise ratio (R^2), a measure of how close measurements and predictions are.

Gregg *et al.* previously applied SCC to the measurement of alfentanil drug effect.[8] They demonstrated in a test population that the EEG-based measurement developed with SCC, the alfentanil canonical univariate parameter (CUP), performed better than spectral edge, median frequency, δ power, θ ratio, and total power as a measurement of alfentanil drug effect on the CNS.

In this article we extend those results to five opioids, alfentanil (in a new data set), fentanyl, sufentanil, trefentanil, and remifentanil, comparing the performance of the CUP to the commonly used EEG parameter, spectral edge, $SE_{95\%}$. The R^2 of the two EEG parameters was statistically compared.

Methods

We used EEG data recorded in prior studies,[2,4,5,9] performed by our research group under the approval of the Stanford University Institutional Review Board. The opioids studied were fentanyl, alfentanil, sufentanil, trefentanil, and remifentanil. The original experiments characterized the pharmacokinetic and pharmacodynamic profile of the opioids using the EEG as a measure of opioid drug effect on the CNS. Alfentanil, trefentanil, remifentanil, and fentanyl[2,9] were studied in healthy volunteers. Additional fentanyl[4] and sufentanil[5] data were used from studies in patients undergoing general anesthesia. The patients receiving sufentanil or fentanyl were ASA physical status 1–2, scheduled for a variety of elective surgical procedures, and who received no premedication or other CNS active drug prior to their EEG study. Demographic characteristics for all these subjects were reported in the respective publications.[2,4,5,9] Details about the drug administration and the EEG endpoints pursued are given in table 1.

Electroencephalographic Data Collection

The details of the EEG data collection are as reported in the original manuscripts[2,4,5,9] and the EEG signal analysis for all five opioids was as described by Gregg *et al.*[8] To compute the CUP, the frequency spectrum of the EEG for each epoch was reduced to 10 bins of 3 Hz each representing the EEG power spanning from 0.5 to 30 Hz. This binning method has higher resolution than the "classical" frequency bands δ, θ, α, and β.

The Canonical Univariate Parameter

The EEG measure reported by Gregg *et al.* is based on a series of coefficients that apply to the spectral powers in the 10 3-Hz frequency bins.[8] It was derived using the SCC technique, described later. The coefficients reported by Gregg *et al.* are shown in table 2.

Figures 1A and 1B show how the EEG measures of drug effect were constructed for a representative baseline EEG waveform (fig. 1A) and a waveform showing maximum opioid drug effect (fig. 1B). This example of maximal EEG effect was obtained by visual inspection of the EEG tracing, looking for maximal opioid-induced slowing. The raw signal was initially digitized and transformed into the frequency domain by means of the fast Fourier transform, obtaining 60 frequency bins of 0.5 Hz each spanning from 0.5 Hz to 30 Hz. The spectral edge was defined as the frequency below which 95% of the power lies, as shown on the second graph in the two figures. The 60 frequency bins were then reduced to 10 bins of 3 Hz each (third graph in figs. 1A and 1B). The power in each bin was converted into a natural log (log) of the power (fourth graph in figs. 1A and 1B). In the last graph in figures 1A and 1B, the log in each bin is multiplied by the corresponding coefficient from table 2. The CUP is then merely the sum of the bins shown in the last graph in figures 1A and 1B. In other words,

$$\mathrm{CUP} = \sum_{i=1}^{10} \gamma_i \log b_i, \qquad (1)$$

where the γ_i are the coefficients taken from table 2, and the b_i represent the power in each one of the ten frequency bins.

Table 2. Values for the Weighting Coefficients Obtained with Semilinear Canonical Correlation for Each Frequency Bin*

Frequency Bin (Hz)	Coefficient (γ)
0.5–3	0.4489
3.5–6	0.2836
6.5–9	0.1865
9.5–12	−0.5256
12.5–15	−0.0683
15.5–18	−0.1269
18.5–21	0.0619
21.5–24	−0.0662
24.5–27	−0.1066
27.5–30	0.1886

*From Gregg *et al.*[8]

Summarizing, the CUP is not only the γ coefficients, but the combination of the logs of the powers and their corresponding coefficients. The coefficients tend to "modulate" the changes in the power spectrum in a way that emphasizes where the drug-induced changes are occurring. For opioids, it is known that the main change is a shift in the power toward the low frequencies, and the combination of the logs of the powers and the coefficients reflects this trend (see bottom panels of figs. 1A and 1B). Thus, it is not as important whether the coefficient for the last frequency bin is positive as it is that the log of the power in that bin multiplied by the coefficient is very small and contributes negligibly to the CUP. Greater CUP values indicate that the effect is increasing.

Pharmacokinetic and Pharmacodynamic Models

The observed drug effect was related to drug concentration at the site of drug effect using a pharmacodynamic model. Previous publications using the EEG as a measure of drug effect have used the classic Hill equation[10] as the model relating concentration in the effect compartment, C_e, to EEG effect, E, as follows:

$$E = E_0 + (E_{max} - E_0)\frac{C_e^{\alpha}}{C_e^{\alpha} + IC_{50}^{\alpha}}, \qquad (2)$$

where E is the effect being modeled, either $SE_{95\%}$ or the CUP, E_0 is the effect when no drug is present, E_{max} is the maximum possible effect reached because of the administration of the drug, IC_{50} is the effect compartment concentration associated with an effect half the difference between E_{max} and E_0, and α is the Hill equation coefficient that determines the steepness of the relationship. The apparent effect compartment concentration, C_e is calculated as

$$C_e(t) = C_p(t) * k_{e0} e^{-k_{e0}t}, \qquad (3)$$

where k_{e0} is the elimination rate constant from the effect compartment,[11] * is the convolution operator, and $C_p(t)$ is the prediction of the pharmacokinetic model at time t. In turn, $C_p(t)$ was calculated as the convolution of the plasma disposition function with the drug input over time, I(t):

$$C_p(t) = \sum_{j=1}^{3} A_j e^{\lambda_j t} * I(t), \qquad (4)$$

where I(t) is the infusion rate shown in table 1 and the duration of the infusion. The values of A_j and λ_j are

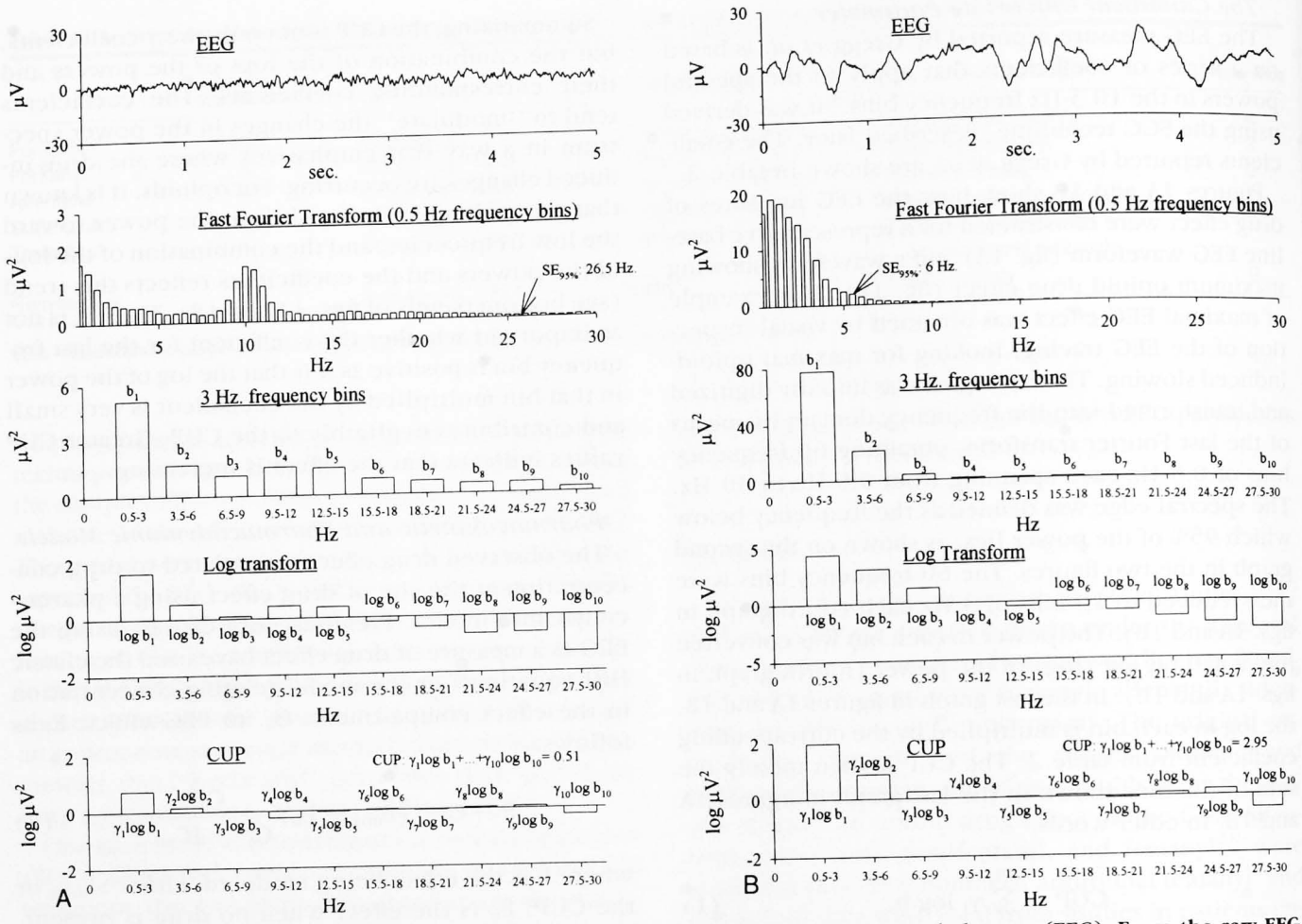

Fig. 1. Construction of the alfentanil canonical univariate parameter of the electroencephalogram (EEG). From the raw EEG signal (graph 1) we obtained the power spectrum by means of the FFT (graph 2). The power spectrum was calculated for each 20 sec epoch of EEG signal (although only 5 sec are shown in graph 1 for clarity). We then added every six bins to obtain ten bins of 3 Hz each (graph 3); the fourth graph shows the log (natural log) transformation of the power in each bin and how the γ vector transformed the power in each frequency bin. (*A*) Baseline EEG. (*B*) EEG during maximal opioid effect. Note in graph 2 the value for the spectral edge and the canonical univariate parameter value in graph 5. Note also in graph (*B*) that the shift in the power toward the lowest frequency bins along with the important decrease in power from b_4 to b_{10}.

those of the individual subjects for the study, either as reported by the authors (fentanyl,[2,4] alfentanil,[2] trefentanil,[2] remifentanil[9]) or as calculated by using extended least-squares regression for each person from the original data (sufentanil[5]).

Nonlinear Regression

Combining the above relationships yielded the following pharmacodynamic model relating the pharmacokinetic parameters, the time course of the infusion, the observed EEG data, and the parameters of the pharmacodynamic model for $SE_{95\%}$:

$$SE_{95\%} = E_0 + (E_{max} - E_0) \times \frac{((\sum_{j=1}^{3} A_j e^{-\lambda_j t} * I(t)) * k_{e0} e^{-k_{e0} t})^{\alpha}}{IC_{50}{}^{\alpha} + ((\sum_{j=1}^{3} A_j e^{-\lambda_j t} * I(t)) * k_{e0} e^{-k_{e0} t})^{\alpha}}; \quad (5)$$

for the canonical univariate parameter:

$$CUP = \sum_{i=1}^{10} \gamma_i \log b_i = E_0 + (E_{max} - E_0) \times \frac{((\sum_{j=1}^{3} A_j e^{-\lambda_j t} * I(t)) * k_{e0} e^{-k_{e0} t})^{\alpha}}{IC_{50}{}^{\alpha} + ((\sum_{j=1}^{3} A_j e^{-\lambda_j t} * I(t)) * k_{e0} e^{-k_{e0} t})^{\alpha}}. \quad (6)$$

Each person was fit separately. The unknown parameters of the above models are IC_{50}, α, E_0, E_{max}, and k_{e0}.

These pharmacodynamic parameters were estimated independently for $SE_{95\%}$ and CUP using nonlinear regression with ordinary least-squares. Because we are trying to maximize correlation between the measure of drug effect and the drug concentration in the effect site, the objective function was the R^2 (coefficient of determination or squared coefficient of correlation, R^2).[12] This coefficient is defined as;

$$R^2 = 1 - \frac{SSE}{SST} = 1 - \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n} (y_i - \bar{y})^2} \qquad (7)$$

where SSE (sum of squared errors) represents the sum of the squares of the differences between the observed measurements y_i for a given time and what the model predicts for this same time, $\hat{y}_i$, and SST (total sum of squares) stands for the sum of the squares of the differences between each actual measurement and the average of all the measurements, $\bar{y}$. Observe that because SST does not depend on the model parameters, maximizing R^2 is equivalent to minimizing SSE, *i.e.*, it is equivalent to nonlinear regression with ordinary least-squares.

The R^2 is a measure of the proportion of the variation in the effect measurement directly attributable to changes in concentration of the drug at the site of drug effect. A value of R^2 close to one means that changes in effect can be entirely explained by changes in the apparent effect compartment concentration. A value of R^2 close to zero means that there is no relationship between effect compartment concentration and effect.[12,13] We compared the values of R^2 between $SE_{95\%}$ and the CUP using the Wilcoxon signed rank sum test for paired values.

Semilinear Canonical Correlation

Semilinear canonical correlation‖ is the statistical approach that allows one to extract from the complex multidimensional EEG recording only the information maximally correlated with "apparent" effect compartment concentration of the drug. The technique is exactly what is described in the regression description for CUP in equation 6, except that the ten coefficients γ_i are estimated concurrently with the parameters of the pharmacodynamic model IC_{50}, α, E_0, E_{max}, and K_{e0}.

In conventional canonical correlation,[14,15] all parameters enter the model linearly. Semilinear canonical correlation differs from conventional canonical correlation only in that several parameters (IC_{50}, α, and K_{e0}) enter the model nonlinearly, and hence a nonlinear regression is required. Figure 2 explains SCC using a progression of more familiar statistical models.

Using SCC, we estimated the elements of the γ vector for each person. We then calculated a population estimate of the elements of the γ vector for each opioid by taking the arithmetic mean of each element of γ

$$y = \beta_0 + \beta x \qquad \text{simple linear regression}$$

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \qquad \text{multiple linear regression}$$

$$\gamma_1 y_1 + \gamma_2 y_2 + \cdots = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \qquad \text{canonical correlation}$$

$$y = \frac{x^{\beta_1}}{\beta_2^{\beta_1} + x^{\beta_1}} \qquad \text{nonlinear regression}$$

$$\gamma_1 y_1 + \gamma_2 y_2 + \cdots = \frac{x^{\beta_1}}{\beta_2^{\beta_1} + x^{\beta_1}} \qquad \text{semilinear canonical correlation}$$

$$\gamma_1 \log b_1 + \cdots + \gamma_{10} \log b_{10} = E_0 + (E_{max} - E_0) \frac{C_e^{\alpha}}{IC_{50}^{\alpha} + C_e^{\alpha}}$$

alfentanil canonical univariate parameter (C.U.P.)

Fig. 2. Different linear and nonlinear statistical models as compared to semilinear canonical correlation and to the alfentanil canonical univariate parameter. The x's are independent variables, the y's are dependent variables and the β and γ are parameters of the models. Also shown the model for the canonical univariate parameter as compared to the semilinear canonical correlation model. The ten γ coefficients, E_0, E_{max}, IC_{50}, α, and k_{e0} should be estimated at the same time trying to maximize the value of R^2 (see text).

‖ Beal SL, Dunne A, Sheiner LB: Estimating optimal linear transformations of a multivariate response to a univariate response with application to semilinear canonical correlation. Technical Report of the Division of Clinical Pharmacology. San Francisco, University of California, San Francisco, 1990.

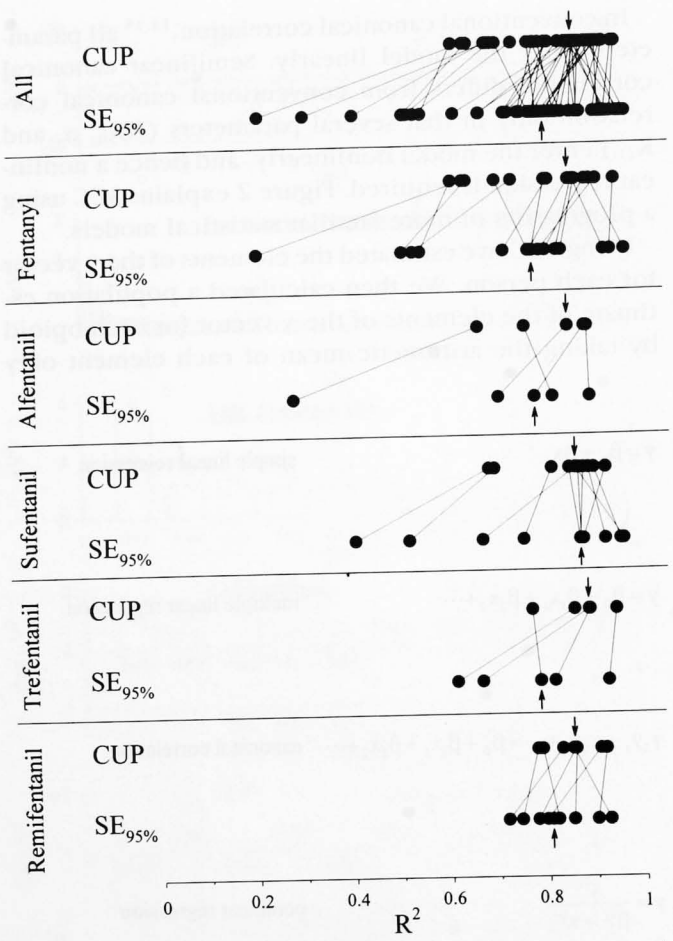

Fig. 3. Signal-to-noise ratio comparison. Values of the signal-to-noise coefficient for both measurements of opioid EEG effect. Every black dot represents a person. The lines connect the value for spectral edge and the canonical univariate parameter in each subject. The small arrows note the median value. The top panel combines the results for all opioids. The lower panels show the results with each opioid individually. Dots overlap where two lines appear to connect to the same dot.

estimated in the persons receiving that opioid. The details of the method are described by Gregg *et al.* We then compared the pattern of the γ vectors among the different opioids to see the extent to which EEG measures customized for each opioid agreed with each other and with the alfentanil CUP.

All the computations for both nonlinear regression and SCC, were performed on a spreadsheet using the Excel software program (Microsoft, Redmond, WA), the parameters were optimized with the Solver tool within Excel. The template spreadsheet is available by anonymous File Tranfer Protocol (FTP) in the /public/scc.dir directory of pkpd.icon.palo-alto.med.va.gov. The data for each person can be found in separate workbooks.

Results

Signal-to-Noise Ratio

One EEG measurement every 20 s (3 measurements per min) were used for fitting; EEG recording time ranged from around 60 min for sufentanil and fentanyl to 2 h for alfentanil, trefentanil, a subset of fentanyl and remifentanil. The same number of data points were used in each person for $SE_{95\%}$, for the CUP and to compute the optimal canonical combination.

Figure 3 shows the R^2 values for each person for $SE_{95\%}$ and the CUP measures of drug effect. The top graph shows the results for all five opioids, while the lower graphs distinguish the different opioids. Every black dot in the plot represents a person and the connecting line tracks the improvement or decrement in the R^2 value. The arrow shows the median value within each drug group.

Figure 3 shows that $SE_{95\%}$ was a good measure of opioid drug effect for the five opioids studied. In general, R^2 was about 0.8 for $SE_{95\%}$ across the opioids studied. The comparison of R^2 between $SE_{95\%}$ and the CUP, when considering all opioids together, yielded an improvement in median R^2 (0.80 *vs.* 0.86) that was statistically significant ($P = 0.0006$; table 3). For fentanyl, a statistically significant difference in R^2 values was also found ($P = 0.02$; table 3). The trend toward improved

Table 3. Values of the Signal-to-Noise Ratio for All the Individuals and for Each Drug for Both $SE_{95\%}$ and the CUP

R^2		Mean	Median	Range
All* (n = 44)	$SE_{95\%}$	0.76	0.80	0.20–0.96
	CUP	0.83	0.86	0.61–0.94
Fentanyl (n = 15)	$SE_{95\%}$	0.72	0.77	0.20–0.96
	CUP	0.80	0.85	0.61–0.94
Alfentanil (n = 5)	$SE_{95\%}$	0.71	0.80	0.30–0.91
	CUP	0.83	0.87	0.68–0.90
Sufentanil (n = 11)	$SE_{95\%}$	0.78	0.87	0.40–0.95
	CUP	0.83	0.86	0.68–0.92
Trefentanil (n = 5)	$SE_{95\%}$	0.76	0.78	0.61–0.92
	CUP	0.87	0.88	0.77–0.94
Remifentanil (n = 8)	$SE_{95\%}$	0.82	0.81	0.72–0.93
	CUP	0.85	0.85	0.78–0.92

$SE_{95\%}$ = spectral edge 95%; CUP = canonical univariate parameter.
* $P = 0.0006$.
† $P = 0.02$.

R^2 was seen for each opioid studied, even in the case of sufentanil were the CUP R^2 was greater for 6 of 11 subjects, as shown in the lower 5 graphs of figure 3.

Perhaps of greater clinical significance was the increased consistency of the CUP when compared with $SE_{95\%}$. For every opioid except remifentanil, there were persons in whom the $SE_{95\%}$ performed relatively poorly (R^2 less than 0.7). In these persons, the relationship of the CUP to effect site concentration was considerably stronger than the relationship of $SE_{95\%}$. Additionally, in no subject was the R^2 value for the CUP less than 0.6. Thus, the CUP behaved as a better measure of drug effect, in that it did not perform abysmally as $SE_{95\%}$ occasionally did. Figure 4 illustrates this point. Here we show the worst examples (by R^2 criterion) of the relationship between concentration and response for $SE_{95\%}$ and CUP for the five opioids and how this same relationship is described by the other parameter. The worst R^2 for every drug was from a $SE_{95\%}$ as can be seen in figure 3. For fentanyl and alfentanil, the CUP found a drug effect while $SE_{95\%}$ found virtually no relationship. For sufentanil, the CUP relationship was somewhat steeper and had less variability about the baseline. For trefentanil and remifentanil, the primary improvement was decreased noise, particularly about the baseline.

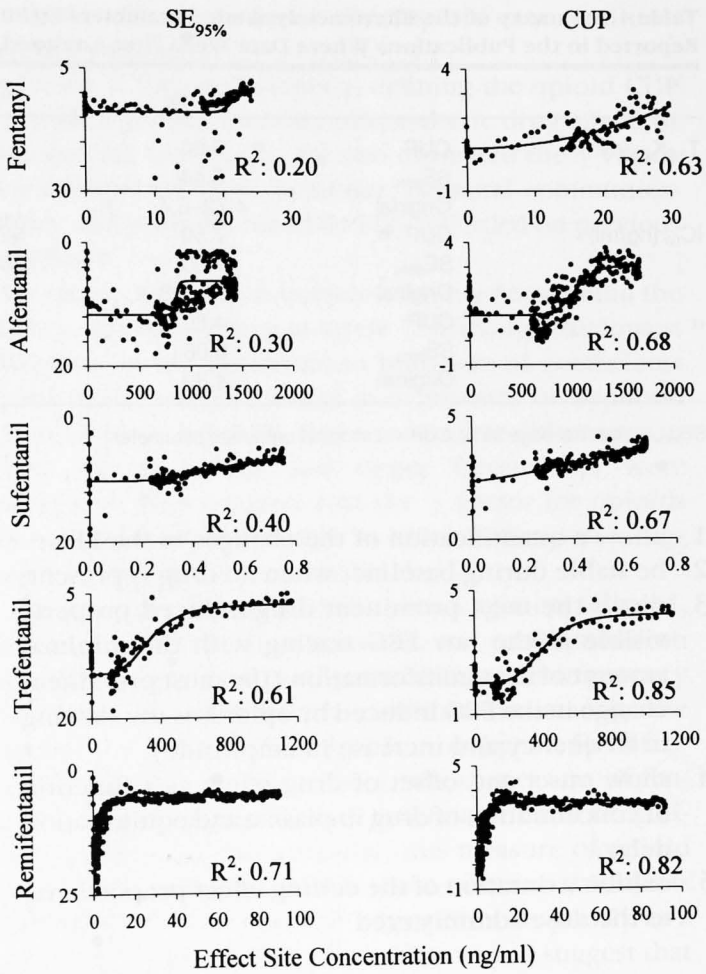

Fig. 4. Effect (vertical axis) *versus* effect site concentration (horizontal axis) relationships in the persons with lowest value for the signal-to-noise ratio. On the graphs at left, $SE_{95\%}$ versus effect site concentration for every opioid is plotted; the corresponding graph on the right shows the relationship between effect site concentration and the canonical univariate parameter for the same person. Each graph also shows the value for signal-to-noise ratio.

Pharmacodynamic Analysis

Of the initial 44 subjects, the concentration-response relationship for both $SE_{95\%}$ and for CUP could be described by a sigmoidal relationship in 33. The subjects where the relationship between effect and apparent effect site concentration did not follow a sigmoidal shape, were not included in the following analysis of the pharmacodynamic parameters. Table 4 shows the values for $t_{1/2}\,k_{e0}$, IC_{50}, and α estimated using the CUP, $SE_{95\%}$, and as reported in the original studies. The values for $t_{1/2}\,k_{e0}$, IC_{50}, and α are generally in good agreement between $SE_{95\%}$ and the CUP, and with the values reported by the original authors. Figure 5 shows the concentration *versus* response relationship for all five opioids, using both measures of drug effect. As expected, the effect site concentration *versus* response relationships estimated using CUP and $SE_{95\%}$ were similar. Thus, CUP appeared to be measuring the same pharmacodynamic phenomenon as $SE_{95\%}$, but with increased R^2.

Optimal Coefficients Estimated Using Semilinear Canonical Correlation

Figure 6 shows the mean γ vector for each opioid, and the γ vector from table 2. The γ vectors for all five opioids are very similar, and follow the same pattern as the γ vector reported by Gregg *et al.* These similarities suggest that the EEG response as a measure of opioid drug effect is consistent across these five opioids. In general, the weights estimated by SCC are greater at the lower frequency bins where most of the opioid effect is located.

Discussion

Bührer *et al.*[16] argue that a suitable EEG parameter for characterizing the C_e *versus* EEG effect relationship should

Table 4. Summary of the Pharmacodynamic Parameters Estimated with Both $SE_{95\%}$ and the CUP as Compared with the Values Reported in the Publications Where Data Were First Analyzed

		Fentanyl	Alfentanil	Sufentanil	Trefentanil	Remifentanil
$T_{1/2}K_{e0}$ (min)	CUP	5.06	0.51	8.13	1.33	0.79
	$SE_{95\%}$	5.44	0.41	7.83	1.59	1.07
	Original	4.72–5.4	0.60	6.20	1.20	
IC_{50} (ng/ml)	CUP	7.50	525.57	0.60	403.63	11.65
	$SE_{95\%}$	7.00	466.82	0.73	336.23	8.51
	Original	8.9–9.8	577.00	0.68	429.00	
α	CUP	4.80	7.57	4.35	5.99	4.27
	$SE_{95\%}$	6.08	7.57	3.70	4.83	2.89
	Original	4.80	6.00	3.10	5.00	

$SE_{95\%}$ = spectral edge 95%; CUP = canonical univariate parameter.

1. allow a quantification of the changes in the EEG;
2. be stable during baseline, when no drug is present;
3. distill the most prominent drug-induced property visible in the raw EEG tracing with the minimal amount of data transformation (the most prominent change in the EEG induced by opioids is the slowing in frequency and increase in amplitude);
4. show onset and offset of drug effect as a function of concentration of drug in plasma and equilibration delay;
5. exhibit a duration of the ceiling effect proportional to the dose administered
6. be obtainable with the use of available software.

In these studies, the CUP met all of the criteria except possibly item 5, which was not specifically investigated. Thus the CUP is a nearly optimal EEG parameter for the purpose of measuring opioid drug effect on the CNS.

In general, $SE_{95\%}$ is also a good measure of opioid drug effect. In the original work by Gregg *et al.*, $SE_{95\%}$ was the best among the standard measurements of drug effect on the EEG evaluated. Additionally, investigators have used $SE_{95\%}$ as a measure of opioid drug effect for longer than 15 yr with good results.

When $SE_{95\%}$ performed well as a measure of drug response, the CUP also performed well and the difference

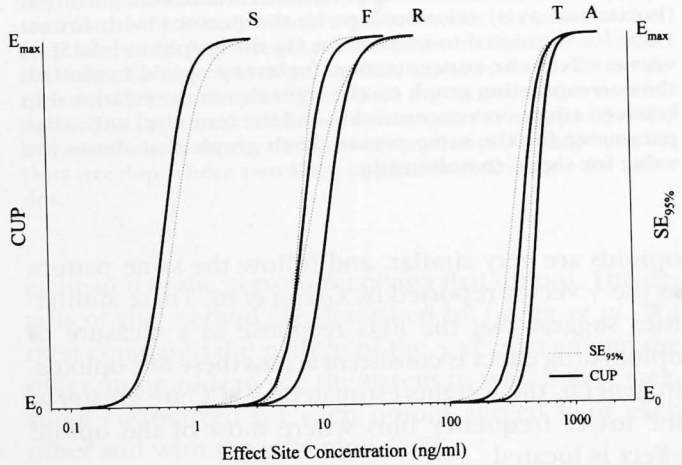

Fig. 5. The canonical univariate parameter and spectral edge *versus* effect site concentration. Based on the pharmacodynamic parameter estimates obtained with both electroencephalographic measures of effect, the graph shows both spectral edge and canonical univariate parameter together for each opioid in a logarithmic scale of effect site concentration. The sigmoidal relationship for spectral edge is preserved when using canonical univariate parameter as a measure of opioid effect.

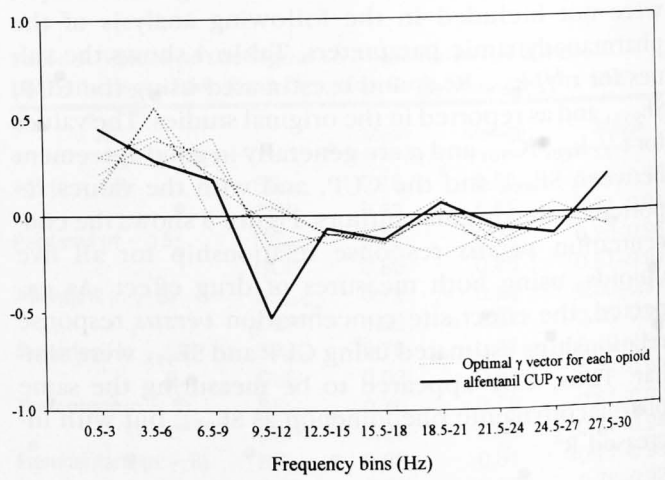

Fig. 6. Opioid γ vector. The comparison between the pattern of the γ vector reported by Gregg et al. and the optimal γ vector for each one of the opioids studied is shown in the graph. In the low frequency range is where the weight of this coefficients is mostly located for all the opioids.

between them was minimal. That the CUP performs better than $SE_{95\%}$ is mostly evident in those persons in whom $SE_{95\%}$ was unable to demonstrate a drug response (figure 4). Since the CUP was designed to maximize the correlation between EEG effect and effect compartment drug concentration, it is able to extract information about drug effect even in noisy EEGs where standard measures fail. The corollary is that the CUP tends to ignore information in the EEG not related to drug concentration. Thus, the CUP can be viewed as a method of noise rejection.

The pharmacodynamic parameters we report differ slightly from those reported by the authors in the original studies (table 4). Modest methodologic differences likely account for why our results were not identical. First, our methods of digitizing and processing waveforms have improved since some of the original studies were performed. To provide consistency across the results, we redigitized the analog signals from all studies not originally processed with our current hardware and software. Additionally, we completely reprocessed the digitized waveforms in all studies so that a consistent processing method applied throughout. These changes in processing accounted for some of the differences in pharmacodynamic results between the original publication and what we report herein. Many of these data sets were originally analyzed using a semiparametric approach to compute K_{e0},[17] whereas we have used a parametric method. These small differences in method likely explain the small differences in pharmacodynamic parameter estimates between this study and the original studies shown in table 4.

We have designed our study as a validation of the univariate parameter designed by Gregg *et al.* In their study they obtained the CUP based on a learning sample of eight persons and tested the resulting coefficients *post hoc* in another sample of seven persons from the same study. We have shown that despite the small size of the learning set (8 persons) and the narrow focus (just alfentanil), this measure of opioid effect on the EEG is applicable to pure μ agonists in general. This is shown not only in our prospective test here with five other opioids, but also by the similarity of the patterns between the γ vector reported in the original article[8] and the γ vector we estimated for each opioid. Thus, we propose that the CUP developed for alfentanil[8] can be generally referred to as the "opioid canonical univariate parameter."

To see if the coefficients γ_i defining the opioid CUP provide a general measure of anesthetic drug effect, or are specific to opioids, we also estimated the γ vector for midazolam (T.W. Schnider, personal communication), and propofol based on EEG recorded on previous studies.#

A visual comparison between these γ vectors and the CUP γ vector is shown in figure 7. Although the lowest frequencies are important to both sets of coefficients (and hence may be useful as a measure of hypnotic drug effect in general), there were clear differences in how the mid-range and upper frequencies were weighted. This suggests that the γ vector for opioids is not generally applicable to other CNS active drugs used in the practice of anesthesia.

In summary, the effect of the pure μ agonists fentanyl, alfentanil, sufentanil, trefentanil, and remifentanil on the EEG is consistent, except for differences in potency and rate of plasma-CNS equilibration among the opioids. A measure of drug effect designed for alfentanil, the CUP, proves to be a robust measure of fentanyl, sufentanil, trefentanil, and remifentanil drug effect on the EEG. In particular, this measure of opioid drug effect performs well in those occasional subjects in whom the 95% spectral edge performs poorly as a measure of opioid drug effect. This would suggest that

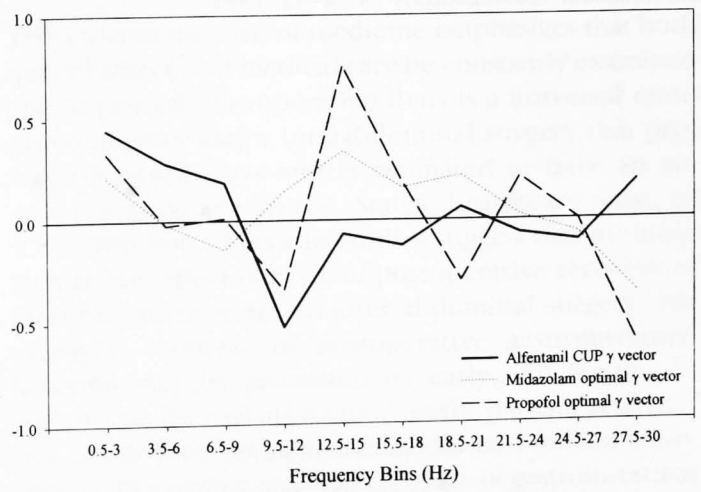

Fig. 7. γ vector of the alfentanil canonical univariate parameter *versus* γ vector for other hypnotics. The pattern of the coefficients from table 2, as compared to the optimal γ vector obtained using semilinear canonical correlation in a group of persons under the effects of propofol or midazolam. Note the different pattern of the weights in the high frequencies for propofol and midazolam as compared to the canonical univariate parameter.

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the CUP may be particularly useful in closed-loop opioid control systems based on an EEG measure of drug response. Such systems must behave well in the worst-case situation, where a poor R^2 might result in inappropriate drug dosing. In addition, our results support the conclusion of Gregg *et al.* that SCC is a useful new statistical tool for developing univariate measures of drug response from the multivariate response measures gathered in clinical research.

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Effects of Perio
Rate of Recove

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Background: Choice of perio
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Methods: Fifty-four patients
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received a preoperative bolus
by an infusion of morphine. G
bolus of bupivacaine followed
Group P received a preoperat

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