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Comparative Pharmacodynamic Modeling of the Electroencephalography-slowing Effect of Isoflurane, Sevoflurane, and Desflurane

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Background: **The most common measure to compare potencies of volatile anesthetics is minimum alveolar concentration (MAC), although this value describes only a single point on a quantal concentration–response curve and most likely reflects more the effects on the spinal cord rather than on the brain. To obtain more complete concentration–response curves for the cerebral effects of isoflurane, sevoflurane, and desflurane, the authors used the spectral edge frequency at the 95th percentile of the power spectrum (SEF_{95}) as a measure of cerebral effect.**

Methods: **Thirty-nine patients were randomized to isoflurane, sevoflurane, or desflurane groups. After induction with propofol, intubation, and a waiting period, end-tidal anesthetic concentrations were randomly varied between 0.6 and 1.3 MAC, and the EEG was recorded continuously. Population pharmacodynamic modeling was performed using the software package NONMEM.**

Results: **The population mean EC_{50} values of the final model for SEF_{95} suppression were 0.66 ± 0.08 (± SE of estimate) vol% for isoflurane, 1.18 ± 0.10 vol% for sevoflurane, and 3.48 ± 0.66 vol% for desflurane. The slopes of the concentration–response curves were not significantly different; the common value was $\lambda = 0.86 \pm 0.06$. The K_{e0} value was significantly higher for desflurane ($0.61 \pm 0.11\ min^{-1}$), whereas separate values for isoflurane and sevoflurane yielded no better fit than the common value of $0.29 \pm 0.04\ min^{-1}$. When concentration data were converted into fractions of the respective MAC values, no significant difference of the C_{50} values for the three anesthetic agents was found.**

Conclusions: **This study demonstrated that (1) the concentration–response curves for spectral edge frequency slowing have the same slope, and (2) the ratio $C_{50}(SEF_{95})$/MAC is the same for all three anesthetic agents. The authors conclude that MAC and MAC multiples, for the three volatile anesthetics studied, are valid representations of the concentration–response curve for anesthetic suppression of SEF_{95}. (Key words: Anesthesia mechanisms; effect compartment; hysteresis.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

THE traditional endpoint used to evaluate potency of volatile anesthetics has been minimum alveolar concentration (MAC), defined as the concentration at which 50% of the patients respond to skin incision with purposeful movement.[1] However, this approach has several drawbacks. MAC does not primarily assess hypnotic properties. In fact, there is evidence that MAC is more related to anesthetic effects on the spinal cord rather than hypnotic effects on the brain.[2,3]

But MAC represents only a single point on a quantal concentration-response curve,[4] and although the MAC concept can be expanded to an entire curve of probabilities (*e.g.*, MAC_{95}, MAC_{99}),[5] it remains a probabilistic function of a quantal response, much steeper than conventional concentration-response curves of continuous parameters.[6] It has not directly been proven that MAC multiples or fractions of MAC represent equal levels of central nervous system (CNS) depression for different anesthetics.

Parameters of the processed electroencephalography (EEG), such as the spectral edge frequency at the 95th percentile of the power spectrum (SEF_{95}) are continuous, nondiscrete values, and therefore an entire concentration time course can be obtained in every patient. Using this parameter, it is possible to compare the concentration-response curves of different anesthetics in

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Table 1. Demographics of the 39 Patients Included in the Study

	Isoflurane	Sevoflurane	Desflurane
Male/female (n)	11/2	11/2	9/4
Age (mean ± SD) (yr)	41.3 ± 16.0	36.2 ± 10.2	40.5 ± 18.9
Weight (mean ± SD) (kg)	74.5 ± 18.0	79.0 ± 12.3	74.3 ± 13.4

terms of potency of the anesthetic (C_{50} value) and shape (slope) of the concentration–response curve. Only if the slopes are identical does the ratio of the C_{50} values describe the potency ratio over the entire range of the concentration effect curve.

For several anesthetic agents, the SEF_{95} has been shown to correlate closely with anesthetic concentrations.[7] In addition, it has been shown to predict the level of consciousness and hypnosis,[8] reflecting the action of anesthetic agents on the brain. Comparing C_{50} values for SEF_{95} changes with the respective MAC values allows us to answer the question as to whether potency comparisons using MAC values are valid when suppression of cerebral function is the endpoint of interest.

We therefore obtained concentration–response curves for the volatile anesthetics isoflurane, sevoflurane, and desflurane and compared the C_{50} values for spectral edge frequency reduction with MAC values.

Methods

After institutional review board approval and informed consent were obtained, 39 patients undergoing elective surgery were included in the study. All patients were classified American Society of Anesthesiologists physical status I or II, as judged by medical history, physical examination, electrocardiography (ECG), chest radiograph, and laboratory results. Patient demographics are shown in table 1.

Study Design

The enquiry was a randomized, prospective, open-label study. The patients were examined prior to surgery. All received 7.5 mg oral midazolam as premedication 60 min prior to induction. No patient needed and received preoperative pain medication or other CNS-active drugs.

After arrival in the induction room, standard monitoring and intravenous access were established. Thereafter the EEG was recorded for 10 min prior to induction to obtain an awake baseline. Patients were instructed to keep their eyes closed and refrain from talking and moving during this period.

Anesthesia was induced using propofol (2.5 mg/kg) and vecuronium (0.1 mg/kg) to facilitate intubation. Anesthesia was maintained with either isoflurane (n = 13), sevoflurane (n = 13), or desflurane (n = 13), as specified in the randomization protocol. Neither opioids nor nitrous oxide were used during the entire study period. End-tidal partial pressure of carbon dioxide ($P_{ET_{CO_2}}$) and nasopharyngeal temperature were monitored continuously to ensure normothermia and normocapnia ($P_{ET_{CO_2}}$ 35–40 mmHg), the arterial blood pressure was maintained within 15% of the preanesthetic value with crystalloid or colloid infusions. To minimize the influence of propofol on the EEG, a 30-min waiting period was imposed prior to data collection. Thereafter, the end-tidal anesthetic concentration of the respective anesthetic was varied according to a randomized sequence of monotonic increases and decreases ("up-down" or "down-up") with constantly changing concentrations between 0.6 and 1.3 MAC (steady-state concentrations were not attempted to be reached). The sequence was repeated, and the EEG was recorded for 20–100 min in each patient. End-tidal anesthetic concentrations were measured using the infrared spectrophotometric analyzer of an anesthesia workstation (Cicero, Dräger, Lübeck, Germany) and recorded in 10-s intervals on a computer hard disk. Surgery commenced immediately after termination of the study.

Electroencephalographic Monitoring and Signal Processing

The EEG was recorded continuously at C3′ or C4′ referenced to Fpz (international 10–20 system of electrode placement), using sterile platinum needle electrodes (Dantec, Copenhagen, Denmark). Electrode impedance was kept below 2 kΩ. EEG recordings were performed with a Dantec Neuromatic 2000 system (Dantec). Analog filters were set at 0.5 and 1,000 Hz. The EEG signal was digitized on an analog–digital converter at 4,096 Hz, filtered digitally at 32 Hz, and stored on a computer hard disk for further off-line analysis at a sampling rate of 128 Hz. Fast Fourier transformation was performed on 8-s intervals, and the SEF_{95} calculated with commercially available software (DASYlab, DATALOG, Moenchengladbach, Germany). The SEF_{95} was then used as a measure of drug effect in the pharmacodynamic model. SEF_{95} values were averaged over four consecutive 8-s intervals, yielding a datapoint every 32 s. The

EEG recordings were visually screened for artifacts (especially eye movements during baseline recording). For each 8-s interval a burst suppression indicator was calculated. After 2 Hz highpass filtering, the 8-s interval was divided into 16 segments, and local variance calculated for each segment. A variance of less than 1 μV was defined as suppression. All intervals with more than four segments of suppression were excluded from analysis.

Pharmacodynamic Analysis

Using the program system NONMEM (University of San Francisco, San Francisco, CA),[9] we modeled the relationship between the end-tidal concentrations of the volatile anesthetics as the independent parameter and the SEF_{95} as the dependent parameter.

To eliminate the hysteresis between the end-tidal concentrations of all volatile anesthetics and the SEF_{95} values, an effect compartment was introduced into the model:

$$dC_{eff}/dt = (C_{et} - C_{eff}) \cdot k_{eo} \quad (1)$$

C_{et}: end-tidal concentrations of the respective volatile anesthetic

C_{eff}: effect compartment concentration of the respective volatile anesthetic

k_{eo}: first order rate constant determining the efflux from the effect compartment

As volatile anesthetics are theoretically able to suppress cortical activity completely when administered in sufficiently high concentrations,[10] the relationship between effect compartment concentration and SEF_{95} as a measure of drug effect was modeled with a fractional sigmoid E_{max} model:

$$E = E_0 \cdot (1 - C_{eff}^{\lambda}/(C_{50}^{\lambda} + C_{eff}^{\lambda})) \quad (2)$$

where E_0 is the measured baseline effect of each individual, C_{eff} is the apparent effect site concentration, C_{50} is the concentration that causes 50% of the maximum effect, and λ describes the steepness of the concentration-response relation.

An exponential model was used to describe the interindividual variability for both k_{eo} and the pharmacodynamic parameters:

$$\theta_{(n,i)} = \theta_{(n,m)} \cdot e^{\eta(i)} \quad (3)$$

where $\theta_{(n,i)}$ refers to the individual value of the respective parameter, $\theta_{(n,m)}$ is the population mean of the parameter, and η_i varies randomly between individuals with mean zero and variance ω^2. The variable η thus represents the difference between the individual and the "typical" individual. Mathematically, ω is the standard deviation of η in the log domain, but when ω is small, it is an estimation of the coefficient of variation of the model parameter.

Due to the small range of measurements, an additive error model was chosen for modeling residual variability.

$$E_{obs} = E_{exp} + \varepsilon \quad (4)$$

E_{obs} refers to the observed value of the spectral edge frequency, E_{exp} to the value predicted based on the end-expiratory concentrations, time, k_{e0}, and the individual pharmacodynamic parameters. ϵ is normally distributed with mean zero and variance σ^2.

The "first order conditional estimation" method[9] included in version IV of NONMEM was used because the linearization used by the first order method results in biased estimates in certain situations.

Covariate Analysis

Covariates evaluated were type of volatile agent and patient age. Population analysis starts with a model containing the smallest number of parameters that can be fitted to the data. In our case, the simplest model included three parameters: a common C_{50} for all three anesthetics, a common slope factor, and a common k_{eo} (and the respective parameters for interindividual variability). Additional parameters (separate values for different anesthetics or an age factor) are then added until further addition does not yield improvement of the goodness of fit.

The Bayesian estimates of the individual pharmacodynamic parameters were plotted against the covariates. Because no nonlinear relationship was detected by visual inspection of the plots, we used only ANOVA and linear regression to identify parameter-covariate relationships to be tested in the population model. Covariates were added one at a time and were kept in the model, if they improved the goodness of the fit, judged by the likelihood ratio criterion,[11] with $P < 0.05$.

Simulations

A simulation of the EEG-slowing effect of volatile anesthetics was performed for 100 subjects to demonstrate the magnitude of interindividual variability in the SEF_{95} response to volatile anesthetics. One hundred sets of individual pharmacodynamic parameters were simulated based on the estimated population means and interindividual variances.

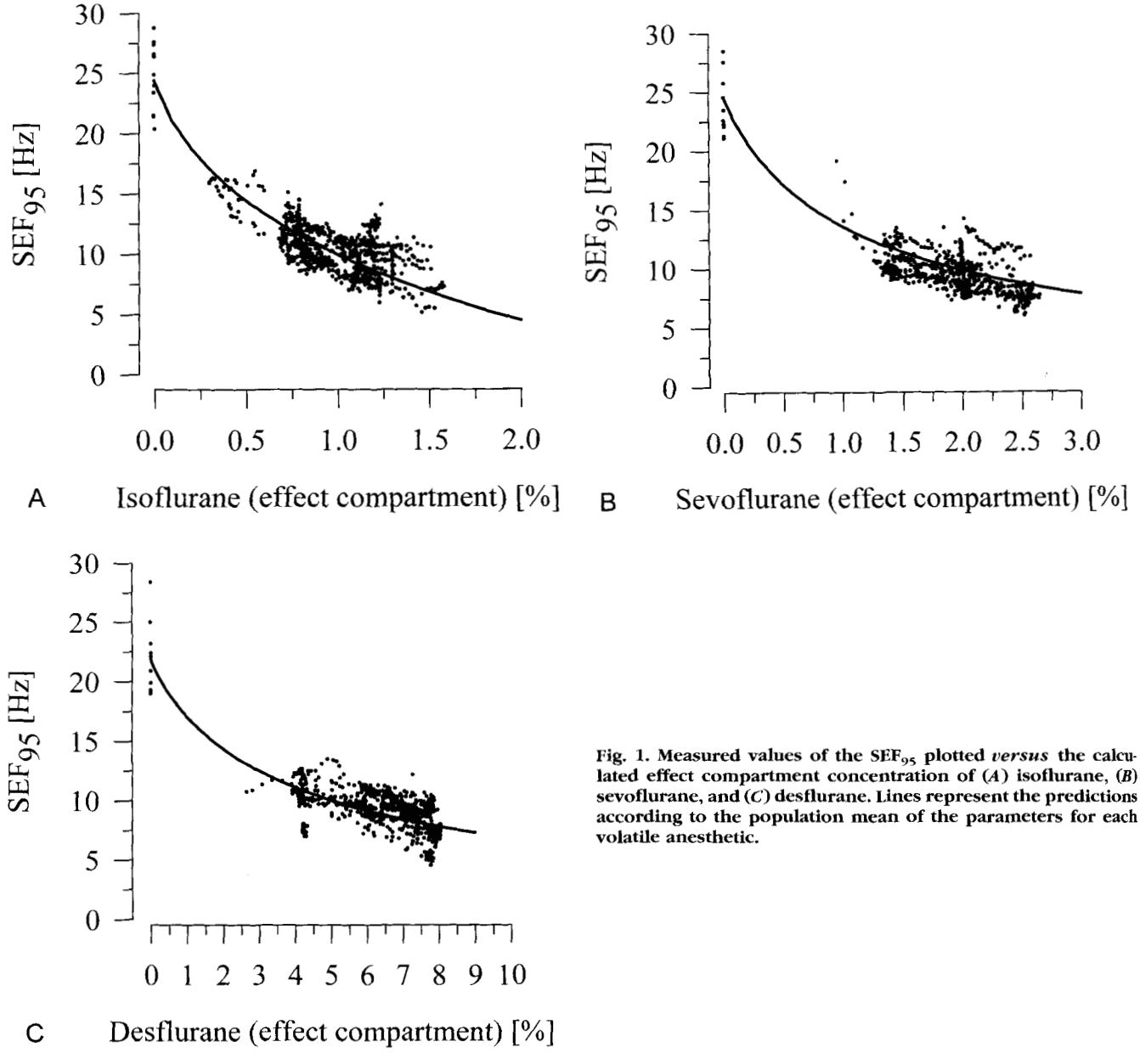

Fig. 1. Measured values of the SEF_{95} plotted *versus* the calculated effect compartment concentration of (*A*) isoflurane, (*B*) sevoflurane, and (*C*) desflurane. Lines represent the predictions according to the population mean of the parameters for each volatile anesthetic.

Results

Patients in the three groups (isoflurane, sevoflurane, and desflurane) did not differ in their demographic variables (table 1, ANOVA). Two patients, one in the sevoflurane and one in the desflurane group, were excluded from the analysis because of noisy EEG data.

The baseline values (mean ± SD) of the SEF_{95} were 24 ± 3, 25 ± 3, and 22 ± 3 Hz for isoflurane, sevoflurane, and desflurane, respectively. Total mean was 24 ± 3 Hz, with no significant differences between the three groups (ANOVA).

A total of 921 datapoints (each being the averaged SEF_{95} from 32 s of EEG recording and the corresponding end-tidal concentration) were usable for analysis in the isoflurane group, 703 in the sevoflurane group, and 889 in the desflurane group.

As expected, it was not possible to fit a model with one common population mean for the C_{50} to the data. Therefore, the simplest model included different C_{50} values for

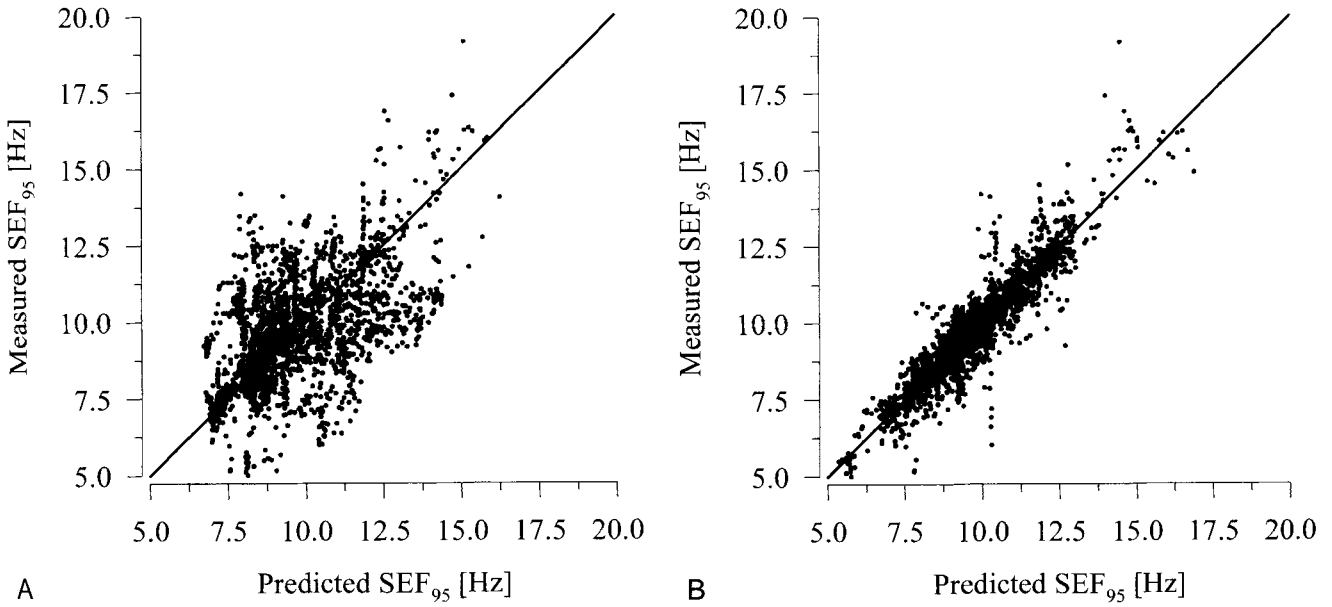

Fig. 2. Adequacy of the phamacodynamic model: predicted *versus* measured SEF_{95} for all patients. The line with the slope of 1 denotes perfect prediction. (*A*) SEF_{95} predicted by the population mean ($r^2 = 0.274$). (*B*) Prediction using the Bayesian estimates of the pharmacodynamic parameters ($r^2 = 0.861$).

each volatile anesthetic, but common population mean values for both k_{e0} and λ. The goodness of fit improved significantly ($P < 0.05$) when a different k_{e0} for desflurane was incorporated into the model. However, permitting different k_{e0} values for sevoflurane and isoflurane did not result in a further improvement of the goodness of fit, neither permitting different λ values.

Figure 1 displays the measured values of the SEF_{95} plotted against the calculated effect compartment concentration of the respective volatile anesthetic. The lines represent the predictions according to the population mean of the parameters for each volatile anesthetic. This plot provides both information about the range of our measurements and the position of the mean prediction in relation to the untransformed data. The goodness of fit has further been assessed by plotting the prediction based on the population model and the prediction with the individual Bayesian parameter estimates versus the measured SEF_{95} (figs. 2A and 2B). The parameters of the final model are given in table 2. The individual Bayesian estimates of the pharmacodynamic parameters are shown in figure 3.

No significant age-dependence was found for any of the model parameters, nor for any single anesthetic agent, nor for the data of all three anesthetics combined (values for the respective parameter were normalized by the population mean of the specific anesthetic agent, as shown for the C_{50} values in figure 4).

To compare the relative potencies of the three anesthetics, concentration values were converted to MAC values. Since mean patient age was approximately 40 yr, we used the MAC values given by Mapleson[12] (1.17% for isoflurane, 1.80% for sevoflurane, and 6.6% for desflurane) for this age to convert the anesthetic concentrations to MAC values.

The population mean C_{50} values for SEF_{95} reduction

Table 2. Pharmacodynamic Parameters of the Final Model

		Isoflurane	Sevoflurane	Desflurane
C_{50} (vol%)	Population mean	0.66	1.18	3.48
	SE of estimate	0.08	0.10	0.66
	Interindividual variability (% CV)		46	
k_{e0} (min^{-1})	Population mean	0.29		0.61
	SE of estimate	0.04		0.11
	Interindividual variability (% CV)		54	
γ	Population mean		0.86	
	SE of estimate		0.06	
	Interindividual variability (% CV)		39	

The percent coefficient of variation (CV) is the square root of the variance of η, and thus only an approximation of the coefficient of variation.

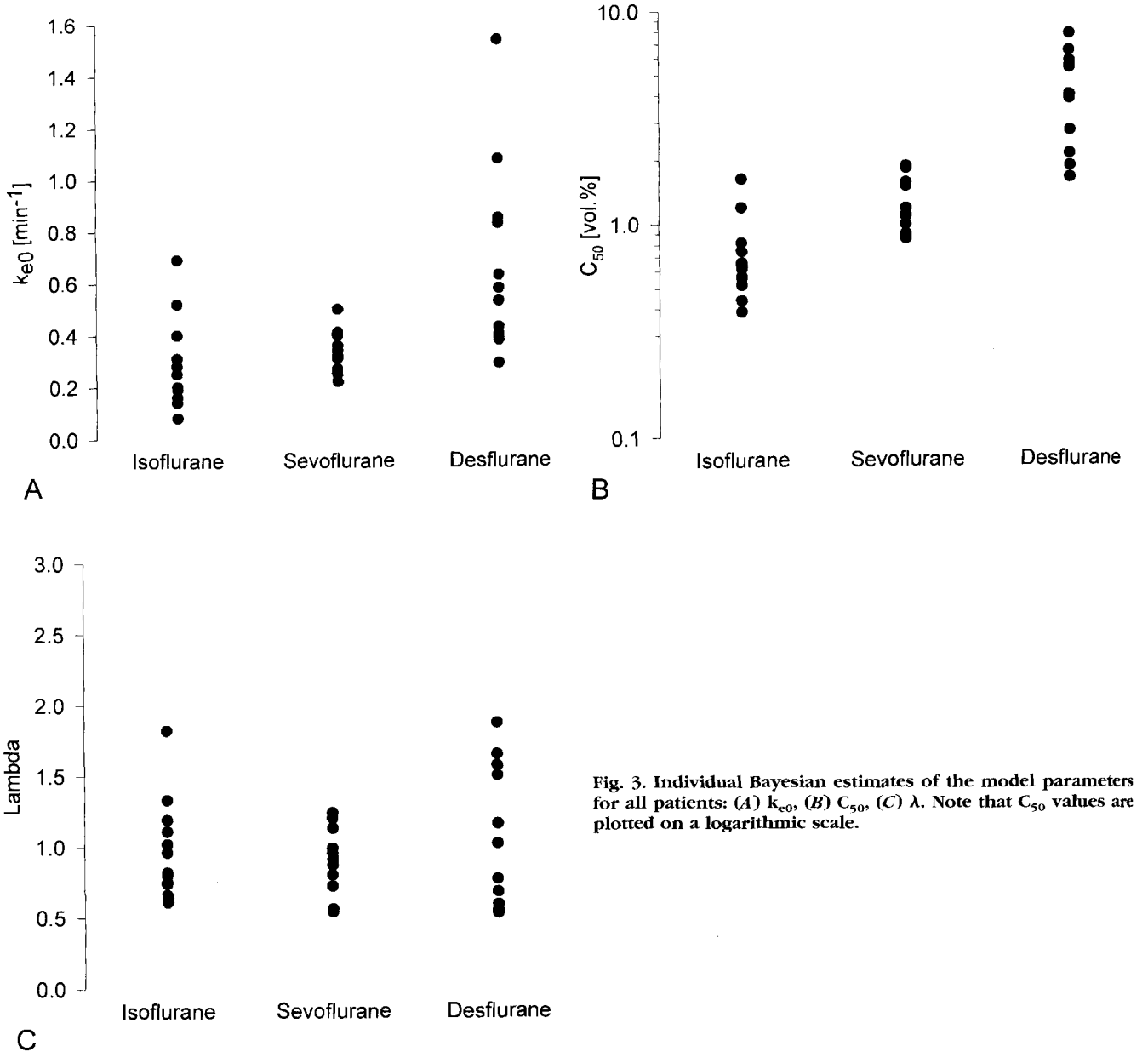

Fig. 3. Individual Bayesian estimates of the model parameters for all patients: (*A*) k_{e0}, (*B*) C_{50}, (*C*) λ. Note that C_{50} values are plotted on a logarithmic scale.

converted to MAC units were 0.56 MAC for isoflurane, 0.65 for sevoflurane, and 0.53 for desflurane.

Using the concentrations converted to MAC units, a model with different C_{50} values for each anesthetic yielded no significant improvement of the goodness of fit, when compared with the simple model with a common population mean for the C_{50} (0.61 MAC with 16–84% quantile 0.46–0.91 MAC).

The simulation of the parameter sets of 100 individuals, using the population mean and the variance of the parameters, yielded the concentration response curves shown in figure 5.

Discussion

This study demonstrates that (1) the relative potency of isoflurane, sevoflurane, and desflurane regarding the EEG-slowing effect is not different from the potency measured by MAC, and (2) that the concentration-

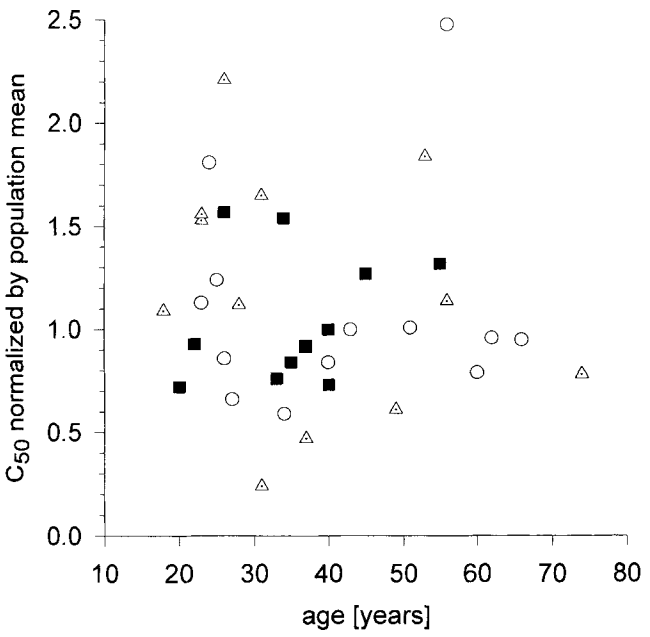

Fig. 4. Individual Bayesian estimates of the C_{50} values for isoflurane (*open circles*), sevoflurane (*filled squares*), and desflurane (*dotted triangles*) *versus* age. For comparison between anesthetics, values are normalized by the population-mean C_{50} value of the specific anesthetic agent.

response relationships of the EEG-slowing effect differ only in potency (C_{50}), as expected, but are otherwise identical for the three anesthetic agents.

Using the end-expiratory concentrations as input for an effect compartment model and relating the measured SEF_{95} to the effect compartment concentrations enabled us to accurately describe the CNS depressant effect of isoflurane, sevoflurane, and desflurane.

Limitations of the Study

Data were obtained under typical clinical conditions from patients, precluding the use of low anesthetic concentrations that might possibly have caused awareness. The influence of propofol used for induction was minimized by the 30-min waiting period. Benzodiazepine premedication, however, may have a longer lasting effect. Nevertheless, the SEF_{95} was in the normal range before induction, and we could not detect a systematic deviation of the predicted *versus* observed values with time. Moreover, we recruited an additional group of five unpremedicated patients anesthetized with sevoflurane following induction with propofol. A NONMEM comparison of these 5 and the 13 premedicated patients of the sevoflurane group yielded no significant difference between the two groups (*i.e.*, permitting different values for C_{50} for both groups did not result in a significant improvement of the fit). The C_{50} values obtained in this analysis (1.26 ± 0.21 vol% for unpremedicated and 1.21 ± 0.10 vol% for premedicated patients) fall both within the standard error of the C_{50} value for sevoflurane yielded by the original analysis of all three anesthetics. Therefore, we consider the effect of midazolam negligible for our analysis.

The concentration range studied was limited by the risk of awareness at the lower end and by the occurrence of burst suppression at the upper end. In a pharmacological sense, this range is only a very small part of the concentration response curve, but it includes the C_{50} values, and it represents the clinically relevant range.

We chose the SEF_{95} and not median frequency as parameter of the processed EEG because the SEF_{95} exhibits larger changes in the concentration range studied (own data, not shown[13]). A preliminary analysis revealed that other parameters such as delta ratio or total power correlated only poorly with anesthetic concentration or exhibited a biphasic concentration-response function. The limitation of burst suppression at higher concentrations could have been overcome by a mathematical correction (burst-compensated SEF[14]). Although this calcu-

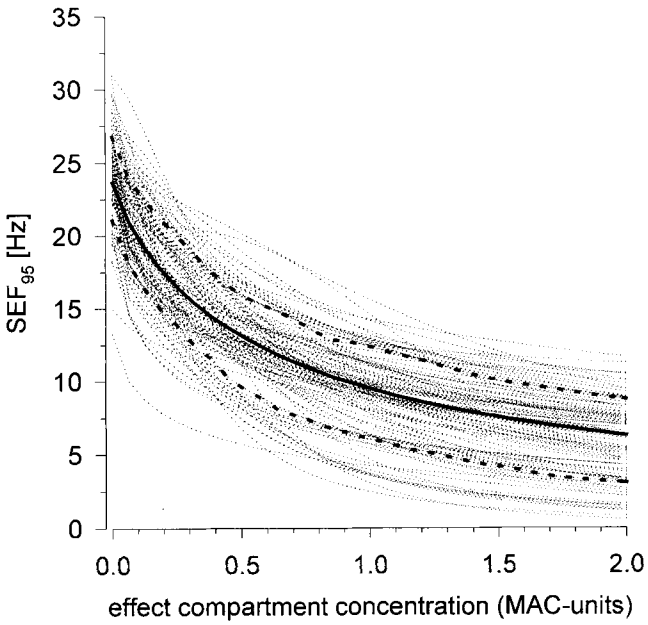

Fig. 5. Simulation of the interindiviual variability of the SEF_{95} response to all three volatile anesthetics studied. Simulated are the parameter sets of 100 individuals, using the population mean and the variance of the model parameters. The effect compartment concentrations are expressed as MAC multiples. The thick line represents the population mean, and the fat dotted lines the confidence interval (16–84% quantiles).

lated variable may measure drug effect even more accurately, the conventional SEF_{95} allowed comparison with pharmacodynamic data for intravenous anesthetics given in the literature.[7,15,16]

The pharmacodynamic model used is restricted by a fixed maximum effect of $SEF_{95} = 0$. Although volatile anesthetics are able to suppress cortical function completely, the signal of the SEF_{95} is lost before reaching a maximum effect due to the occurrence of burst suppression, and thus it may be questioned that the maximum effect is really a SEF_{95} of zero. However, using our data, we were not able to fit a model with the maximum effect as an unconstrained parameter with NONMEM.

Considering the shallow age-dependence of MAC values in adult age (6% change per decade[12]), it is not surprising that we were not able to detect an age-dependence of the parameters on our data. Most individual studies of MAC fail to show a significant age-dependence when analyzed separately; only when data from several studies are combined (or the study specifically included children and elderly patients) could the well-known age-dependence of anesthetic potency be detected.[12] Therefore, a larger sample size or a more extreme age distribution of the sample would be required to specifically test the age-dependence of the $C_{50}(SEF_{95})$ or other pharmacodynamic parameters.

Implications of the Study

When expressed as MAC-multiples, the three anesthetic agents did not differ in their C_{50} values for SEF_{95} reduction. This cannot be assumed *a priori*. SEF_{95} measures an effect on the brain, whereas MAC presumably represents an effect on the spinal cord.[2,3] In fact, it has been reported that halothane reduces EEG frequencies in dogs less than equal MAC concentrations of isoflurane.[17]

For propofol, the $C_{50}(SEF_{95})$ is 4.5 μg/ml,[7] and the Cp_{50} (skin incision) is 8.1 μg/ml,[18] yielding a ratio of 0.55. This is in the same range as the ratio of 0.64 between $C_{50}(SEF_{95})$ and MAC found in this study, although a comparison of values from different studies is difficult. For the three volatile agents studied here, however, awake MAC values are also a constant fraction of MAC for the anesthetic agents studied here,[19,20] supporting the notion that cerebral suppression parallels spinal cord suppression.

The finding that not only C_{50} values (expressed as MAC multiples) but also the slopes of the concentration-response curves cannot be distinguished statistically implies that multiples of the C_{50} will have the same effect on SEF_{95} for all three anesthetic agents. This is a justification of the use of MAC multiples, which denote multiples of effect independent of the anesthetic agent used. Obviously, this needs to be verified for all other volatile anesthetics as well. In addition, this is consistent with a common mechanism of action of these three anesthetic agents for this effect.

It may seem surprising that sevoflurane and isoflurane have statistically indistinguishable k_{e0} values and thus equilibration time constants in our model. However, unlike the clinical situation, our model comprises only the equilibration time course from alveolar space to the effect compartment (presumably the brain), but not the equilibration between inspired and alveolar gas concentrations, which essentially determines the speed of induction.

The equilibration between alveolar gas and brain, however, is determined by both the blood-gas and the brain-blood partition coefficients. Both are lower for desflurane than for the other two anesthetic agents.[21] Although sevoflurane has a much lower blood-gas partition coefficient than isoflurane (yielding faster anesthetic induction because of rapid equilibration between inspired and alveolar concentration), the brain-blood partition coefficient of sevoflurane is actually higher than isoflurane,[22] explaining the similar kinetics of equilibration between alveolar gas and effect compartment.

The simulation of the variability of the SEF_{95} response to volatile anesthetics (fig. 4) allows the evaluation of the usefulness of the SEF_{95} to distinguish certain levels of anesthesia. The differentiation between the nonanesthetized state and 0.6 MAC is feasible despite the variability: at 0.6 MAC, median SEF_{95} is 11.5 Hz, and interindividual variability, expressed as 16-84% quantile (because of the exponential error model used), is 8.0-14.5 Hz, which is out of the variability range for nonanesthetized patients (21.0-26.8 Hz). On the other hand, the SEF_{95} will not allow to distinguish patients at 1.0 and 1.3 MAC (50% and 95% probability of no response to skin incision): at 1.0 MAC, median SEF_{95} is 8.8 Hz, with 16-84% quantiles of 5.6-11.8 Hz; at 1.3 MAC, median SEF_{95} is 7.8 Hz (16-84% quantiles 4.8-10.9 Hz). The difference of the median SEF_{95} at 1.0 and 1.3 MAC is much smaller than the interindividual variability. Therefore, the SEF_{95} cannot be a useful parameter to predict the response to painful stimuli. This has been confirmed for sevoflurane in a recent study assessing the predictive value of EEG parameters for sedation and anesthesia.[8] Interestingly, in this study at concentrations higher than 1.5 vol% no further reduction in SEF_{95} was seen. This is at variance

with our findings, but more importantly, in both studies SEF_{95} in this concentration range does not allow a prediction of sevoflurane concentration.

In summary, we have shown that the concentration-response curves for CNS depression of different volatile anesthetics measured by SEF_{95} can be adequately described, at least in the clinical concentration range, with a fractional sigmoid E_{max} model, using effect compartment concentrations rather than end-tidal concentrations as independent variable.

The ratios of the C_{50} for CNS depression measured by the SEF_{95} to the respective MAC are not different for isoflurane, sevoflurane, and desflurane. Furthermore, since the shape of the concentration-response curves is statistically indistinguishable, it can be concluded that altering the concentration of any of these anesthetic agents for a given fraction of the respective C_{50} will lead to an identical alteration of the effect on SEF_{95}. Although not assessing the CNS effects of anesthetics, MAC is a useful endpoint for the comparison of volatile anesthetics, and the above findings yield a justification of the use of MAC multiples.

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