Anesthesiology
67:341–347, 1987

Closed-loop Feedback Control of Methohexital Anesthesia by Quantitative EEG Analysis in Humans

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A combined pharmacokinetic and pharmacodynamic model of methohexital was used to establish and evaluate feedback control of methohexital anesthesia in 13 volunteers. The median frequency of the EEG power spectrum served as the pharmacodynamic variable constituting feedback. Median frequency values from 2–3 Hz were chosen as the desired EEG level (set-point). In 11 volunteers, the feedback system succeeded in maintaining a satisfactory depth of anesthesia (*i.e.*, unresponsiveness to verbal commands and tactile stimuli). During feedback control, 75% of all measured median frequency values were in the preset range of 2–3 Hz. This distribution of median frequency was obtained by applying random stimulation (six different acoustic and tactile stimuli) to the volunteers approximately every 1.5 min. The decrease of median frequency from baseline to anesthetic values was primarily induced by increasing the fractional power in the frequency band of 0.5–2 Hz from 12.6 ± 4.5% (mean ± SD) to 46.0 ± 2.5%. The median time to recovery (as defined by opening eyes on command) after cessation of the feedback control period was 20.6 min (10.7–44.5 min) when median EEG frequency was 5.2 Hz (4.7–8.4 Hz). The average requirement of methohexital (mean ± SD) during the 2 h was 1.02 ± 0.16 g. It is concluded that pharmacokinetic-pharmacodynamic models of intravenous anesthetics established previously may be used to form a suitable background for model-based feedback control of anesthesia by quantitative EEG analysis. This approach gives a possible solution to the problem of adapting pharmacokinetic and pharmacodynamic data to individuals when using population mean data as starting values for drug therapy. (Key words: Anesthetics, intravenous: methohexital. Monitoring: electroencephalography. Pharmacodynamics: depth of anesthesia. Pharmacokinetics: adaptive feedback control; models.)

PHARMACOKINETIC MODELING provides a useful tool for determining drug administration. By describing the relationship between dose, time, and plasma concentration, such modeling can help determine the most appropriate dosing regimen for particular time requirements.

Several devices have been proposed for automatically controlling drug administration on the basis of pharmacokinetic models.[1–3] Such systems use mean pharmacokinetic data derived for a population to approximate the needs of the individual patient. This mode of controlling the rate of drug administration is commonly called open-loop control. Drug concentrations can hardly be measured in real time for subsequent feedback to the system. For corrections for interindividual variability, the anesthesiologist has to interfere with the system by controlling the set-point of drug concentration interactively.[4] Although it is a step forward in the process of using rational grounds for dosing, several factors have to be considered.

First, the control of plasma concentrations is only an intermediate step in controlling the pharmacodynamic response, the ultimate goal of drug therapy. Second, because interindividual variability is inevitable, these strategies for drug administration use only an approximation of the true dose-response relationship that exists for the individual patient. The true relationship can be better approximated if the response to drug administration is fed back to the drug delivery system.

Recent integrated models of pharmacokinetics and pharmacodynamics have incorporated major aspects of drug action.[5–11] These models require a measurement of drug effect. Because the electroencephalogram (EEG) is a noninvasive, continuous measure of drug effect on the brain, it is a potentially useful physiologic indicator of depth of anesthesia. The early work of Bickford *et al.*[12,13] and Bellville *et al.*[14,15] used the integrated total power of the filtered EEG as a quantitative derivation of depth of anesthesia. More recent investigations dealing with the pharmacokinetic and pharmacodynamic modeling of intravenous agents use frequency-dependent EEG derivations, such as median frequency[8,11,16] or edge frequency,[7,10,17] of the EEG power spectrum. Both measures have been shown essentially to decrease as drug concentrations and depth of anesthesia increase. Thus, if the EEG is a clinically useful measure of drug effect, one should be able to use this information to optimize administration of anesthetic drugs.

Control theory distinguishes between open-loop control and closed-loop control.[18] In open-loop control, the input to the system (*e.g.*, drug dosage) is independent of the output (*e.g.*, depth of anesthesia). In closed-loop control systems, the input at any particular time depends on the previous output. Both control systems require a controller to determine the optimum dosage strategy. This might be the anesthesiologist and/or a model of the process to be controlled (*e.g.*, depth of anesthesia). When the input to the system is controlled by a model, this control is commonly referred to as being "model-based." Model-based, closed-loop control systems may use the measured output of the system not only to determine the next input, but to update the model describing the relationship between input and output. This method is called "model-based and adap-

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Received from the Institut für Anästhesiologie, Rheinische Friedrich-Wilhelms-Universität, Sigmund Freud Strasse 25, D-5300 Bonn 1, Federal Republic of Germany. Accepted for publication April 6, 1987. Presented in part at the ASA Meeting, Las Vegas, 1986.

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tive." Among the models used, one can distinguish between heuristic and deterministic models. PID (proportional-integral-differential) control is a very often used heuristic model for feedback control. In this case, it is assumed that the input to the system needed to correct for a difference between measured output and set-point is related to the difference between the set-point and the output itself, the integral of the output as well as its derivative. Pharmacokinetic-pharmacodynamic models are examples of deterministic models used to control drug dosage. In this context, the early work of Bickford *et al.*[12,13]‡ and Bellville *et al.*[14,15] on the automatic control of drug administration by electroencephalographic means can be classified as using essentially PID-based, nonadaptive, closed-loop control. Later investigations of Cosgrove and Smolen§ used PID-based, adaptive, closed-loop control of thiopental in rabbits.

This study evaluates the applicability of pharmacokinetic-pharmacodynamic models for model-based, adaptive feedback control of methohexital anesthesia as assessed by quantitative EEG analysis. Such analysis uses median EEG frequency as a continuous measure of the action of methohexital on the brain.

Methods and Materials

Subjects and Protocol

We obtained informed consent and institutional approval to study 13 healthy volunteers (22–29 yr, 44–85 kg, 158–186 cm). Four EEG leads (C_z–F_i; C_z–O_i i = 1,2) were amplified (Mingograph Junior®, Siemens) and recorded on magnetic tape (PR 2200®, Ampex). The C_z–O_i i = 1,2 lead having the lower impedance was used for deriving the feedback signal. Prior to methohexital infusion and the feedback control period, the volunteers listened to music *via* earphones to smooth induction of anesthesia and to lessen the awareness of the start of infusion.

After recording the baseline EEG, feedback control of methohexital was begun and maintained for 2 h. During the feedback control period, volunteers were exposed randomly to stimulation consisting of six kinds of stimuli: acoustic sensations, verbal commands, cold stimuli, pin pricks, and testing of eyelid and corneal reflex approximately every 1.5 min. The first two subjects were treated slightly differently. Volunteer 1 received no stimulation at all. Volunteer 2 was given train-of-four stimulation every 20 s for the first hour, and, thereafter, random stimulation. The electrocardiogram and blood pressure (Dinamap®, Critikon) were also monitored. Blood samples from a capillary in the ear lobe were taken every 20 min for blood gas analysis.

EEG Analysis

The filter settings of the EEG amplifier were 0.3 s and 70 Hz. Prior to A/D conversion, the signal was analog filtered between 0.5 and 32 Hz, segmented into epochs of 8.192 s, and digitized at a rate of 125 Hz with 12-bit A/D resolution. For each epoch, the power spectrum between 0.5 and 32 Hz was calculated using common Fast-Fourier-Transformation (FFT) algorithms,[19] from which the median EEG frequency (50% quantile) of the power spectrum was derived. In addition, off-line analysis included calculation of fractional power in the frequency bands 0.5–2 Hz, >2–5 Hz, >5–8 Hz, >8–13 Hz, >13–32 Hz, edge frequency, and mean amplitude. For data smoothing, a moving average of nine epochs was performed.

Administration Device and Algorithm

An infusion pump (IP 4®, Vickers) was attached to the computer (Plurimat PS 300®, Intertechnique) by electronically bypassing the digital switches. A solution of 12 mg of methohexital per milliliter of saline was used to keep the maximum rate of methohexital administration possible with the infusion pump below 20 mg/min. The solution was administered through an indwelling catheter placed in a forearm vein. The procedure was begun with a 4-min infusion of 80 mg of methohexital that was used for estimating initial corrections to the model parameters of the pharmacokinetic-dynamic model. The subsequent rates of methohexital infusion were determined on the basis of the feedback signal and pharmacokinetic-dynamic model used for methohexital. A linear model described by a biexponential disposition function c(t) after iv bolus administration was assumed to represent a valid pharmacokinetic model:[20,21]

$$c(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

The pharmacodynamic response E (median EEG frequency) was related to concentrations by the following sigmoid inhibitory E_{max} pharmacodynamic model:[22]

$$E = E_0 - E_{max}\frac{c^\gamma}{c_0^\gamma + c^\gamma} \text{ ®}, \quad (2)$$

where E_0 is the baseline median value, E_{max} its maximum decrease, c the concentration of methohexital, and c_0 the concentration at half maximal effect. γ describes the steepness of the concentration-response curve. As initial values of the parameters of the pharma-

‡ Bickford RG, Myers RR, Stockard JJ, Kalichman M, Saidman LJ: Remote computerized control of thiopental anesthesia (servo-anesthesia), Proceedings of the Symposium for Biomedical Engineering, vol. 12. Western Periodicals, North Hollywood, 1973, pp 195–197.

§ Cosgrove RJ, Smolen VF: Systems for automatic feedback-controlled administration of drugs: Analog and digital optimal-adaptive control of thiopental anesthesia, Proceedings of the Symposium for Biomedical Engineering, vol. 17. Western Periodicals, North Hollywood, 1978, pp 261–275.

cologic model given by formulas 1 and 2, the following data were used: A = 4.4 mg/l, B = 0.49 mg/l, α = 0.178/min, β = 0.0048/min, c_0 = 3.4 mg/l, γ = 2 (unpublished data) obtained in a previously performed open-loop study.[23] For E_0 and E_{max}, we chose the values 9 Hz and 8 Hz. The rationale for this choice was that an alpha-type baseline EEG exhibits typical median EEG values between 8 and 10 Hz; whereas, at median values below maximum effect, $E = E_0 - E_{max}$ = 1 Hz, one may observe a burst-suppression pattern[8] that violates the assumption that quasistationarity underlies spectral analysis.[24] We chose the interval 2–3 Hz as the desired EEG level (set-point).

A first update of the pharmacokinetic parameters was performed after the initial period of 4 min. Subsequently, we used the following algorithm. If the median EEG value was 2–3 Hz, an infusion scheme was used to maintain the current methohexital concentration, and thus effect, as predicted by the pharmacokinetic model on the basis of the updated model parameters. This method is called the "BET infusion scheme," because it consists of an initial bolus (B) for filling up the initial volume of distribution, a maintenance infusion rate that compensates for elimination (E), and an exponentially declining infusion rate that compensates for transfer (T) of drug into the peripheral compartment.[1,2,25] If the median EEG value was outside this range of values, the difference between measured and predicted values (ΔE)

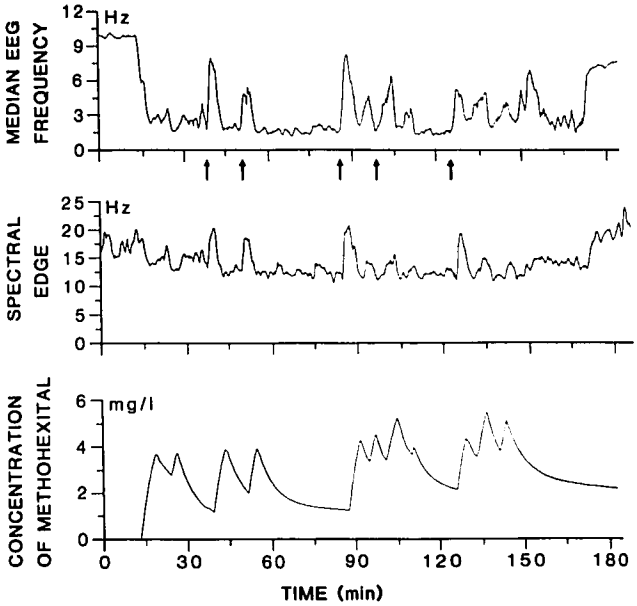

FIG. 1. Electroencephalographic tracings for volunteer 1, who was given methohexital anesthesia and no stimulation. Upper trace: time course of median EEG frequency during feedback control of methohexital infusion. Middle trace: time course of spectral edge frequency. Lower trace: prediction of blood levels of methohexital based on the actual administration of methohexital and mean model parameters. Arrows mark events of spontaneous awareness.

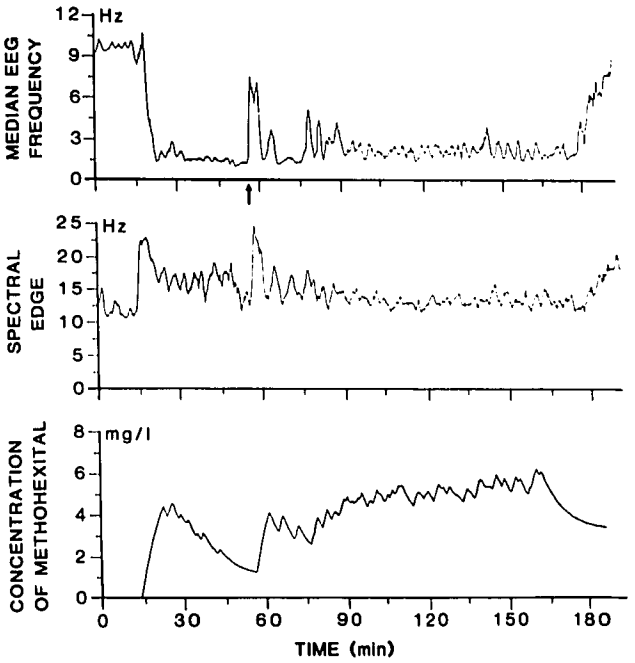

FIG. 2. Electroencephalographic tracings for volunteer 2, who was given methohexital anesthesia, train-of-four stimulation every 20 s for 1 h, and, after minute 75, a number of different stimuli delivered randomly. Upper trace: time course of median EEG frequency during feedback control of methohexital infusion. Middle trace: time course of spectral edge frequency. Lower trace: prediction of blood levels of methohexital based on the actual administration of methohexital and mean model parameters. Arrow marks event of spontaneous awareness.

was used to correct the model parameters. The updated values were used to calculate a new infusion scheme for achieving and maintaining the concentration of methohexital that would induce a median frequency of 2.5 Hz.

This cycle was performed for every EEG epoch (8.192 s) (see Appendix).

Results

Figure 1 depicts the time course of the median frequency, edge frequency, and predicted concentrations of methohexital for volunteer 1 (no stimulation). This volunteer awoke spontaneously five times during the feedback period; on four of these occasions, the predicted blood concentrations of methohexital decreased to below the c_0 value of 3.4 mg/l. Each time, the feedback control reacted promptly and reversed the increase in median frequency.

Figure 2 shows the results for volunteer 2, who was given train-of-four stimulation every 20 s for 60 min. One incident of arousal was observed. After 75 min, the random stimulation was applied. Stable values for median EEG frequency, and nearly constant predicted blood levels of methohexital resulted.

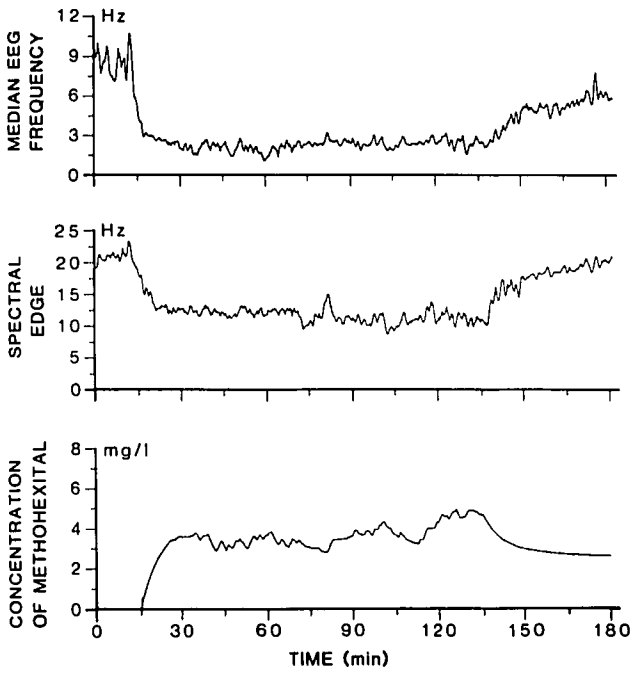

FIG. 3. Electroencephalographic tracings for volunteer 3, who was given methohexital anesthesia and random stimulation over the entire feedback period. Upper trace: time course of median EEG frequency during feedback control of methohexital infusion. Middle trace: time course of spectral edge frequency. Lower trace: prediction of blood levels of methohexital based on the actual administration of methohexital and mean model parameters.

For the other 11 volunteers, random stimulation was applied during the entire feedback cycle. No excitation phenomena during induction of anesthesia were seen. The mean time (±SD) to reach the target range of 2–3 Hz was 9.6 ± 5.2 min, during which time the mean (±SD) dose of methohexital was 192 ± 103 mg. Figure 3 shows the time course of median EEG frequency, edge frequency, and predicted concentration of methohexital for the first volunteer stimulated randomly over the entire feedback period (*i.e.*, volunteer 3). The average time course of median EEG frequency for volunteers 3–13 and its standard deviation during the feedback period and recovery is shown in figure 4. Seventy-five percent of all observed median EEG frequency values during feedback lay within the range of 2–3 Hz. The 90% quantile of the median distribution lay within the range 1.5–3.5 Hz. The cumulative amount of methohexital necessary to keep the median EEG frequency within the target range is given in figure 5. Table 1 provides values for the time to recovery (as defined by opening of the eyes on command), the time required for orientation with regard to time and location, and the median EEG frequencies associated with these two times. Table 2 provides baseline and feedback control values for fractional power in the indicated EEG frequency bands, the median EEG frequency, the spectral edge frequency, and the mean amplitude for volunteers 3–13. The most prominent frequency shift can be

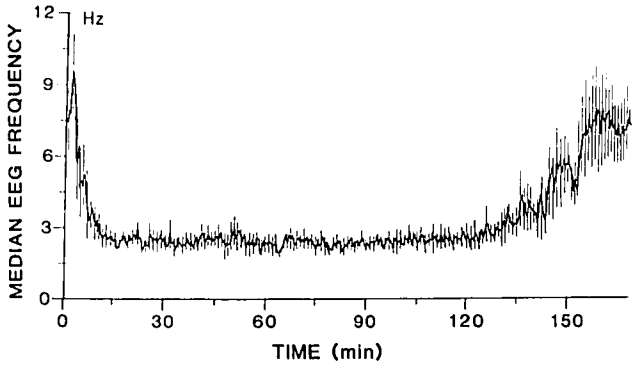

FIG. 4. Group average of median EEG frequency (mean ± SD) during feedback control of infusion of methohexital (0–120 min) in 11 volunteers stimulated randomly over the entire feedback period. The desired range of median EEG frequency was 2–3 Hz.

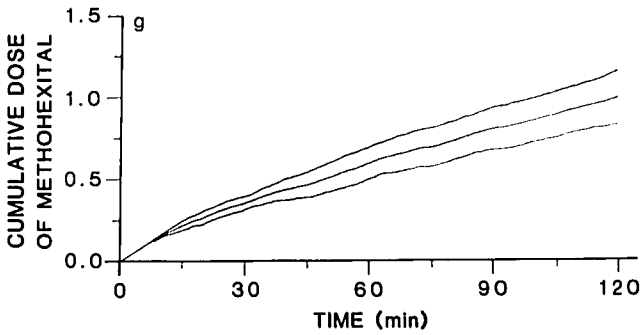

FIG. 5. The mean (±SD) cumulative dose of methohexital required to keep the median EEG frequency from 2–3 Hz in 11 volunteers.

TABLE 1. Time to and Associated Median EEG Frequencies for Clinical Endpoints after Cessation of Feedback Control of Methohexital Anesthesia in 11 Volunteers

Volunteers	Time to Opening of Eyes on Command (min)	Median EEG Frequency (Hz)	Time to Orientation* (min)	Median EEG Frequency (Hz)
3	22.2	5.4	57.4	7.2
4	20.9	4.8	37.5	6.3
5	33.9	5.0	54.6	6.9
6	17.9	5.2	45.9	8.7
7	37.9	7.9	44.4	8.6
8	15.7	5.3	33.5	6.2
9	20.6	8.4	29.4	9.3
10	44.5	5.1	68.1	6.5
11	12.4	5.6	16.8	9.1
12	10.7	5.1	11.7	6.4
13	19.8	4.7	42.7	7.8
Median	20.6	5.2	42.7	7.2

* With respect to date and location.

observed for the lowest frequency band (0.5–2 Hz), which contained an average of 46 ± 2.5% of total power.

Discussion

This study demonstrates the applicability of model-based adaptive feedback control by quantitative EEG analysis for methohexital-induced anesthesia. The desired EEG level (set-point) of median EEG frequency was chosen on the basis of previous investigations with open-loop methods.[23] From a clinical point of view, this set-point was intended to represent the existence of a safe hypnotic effect. Experience with other drugs, such as etomidate[8] and isoflurane,[16] have shown that median EEG values above 5 Hz might be associated with awareness. The results obtained during recovery from methohexital administration in this study (table 1) give support that this is also true for methohexital. In addition, in the first two volunteers, awareness during the feedback period was accompanied by a transition from median values below 5 Hz to values above 5 Hz. Although the feedback system reacted promptly and properly to these events, the basic question remains as to why the therapeutic goal was achieved more efficiently in those subjects stimulated randomly than in those given no stimulation at all or a repetitive train-of-four stimulation.

Stimuli can induce arousal reactions in anesthetized humans[26] which is accompanied by an increase in EEG frequency.[26,27] To maintain a given median EEG frequency can thus require a higher concentration of methohexital in stimulated subjects than in nonstimulated ones, and the higher concentration may have prevented awareness. This explanation, however, cannot clarify the observations made in volunteers 1 and 2 that there are time periods of 15–30 min with no methohexital infusion and stable low median frequency.

Two other aspects of this problem deserve discussion. First, the chosen model and its underlying assumptions may not be appropriate for the nonstimulated subjects. Second, the special values of the model parameters may not be valid. However, because the algorithm is basically adaptive, it is unlikely that the last possibility is true. For volunteer 1, there was an interval of 30 min with no infusion during the period between the first and second episodes of arousal. For this time period, median frequency remained stable, although no reasonable choice of pharmacokinetic parameters would yield constant concentrations of methohexital. Homer and Stanski[17] have shown that a finite (albeit small) amount of time is required for equilibration of thiopental between blood and brain. When coupled with a steep slope in the concentration-response curve, this hysteresis could allow awakening at a time when the controller

TABLE 2. Fractional EEG Power, Median Frequency, Spectral Edge, and Mean Amplitude during Base Line (B) and Feedback (F) Periods in 11 Volunteers

Volunteer	Fractional EEG Power (%)										Median Frequency (Hz)		Spectral Edge (Hz)		Mean Amplitude (uV)	
	0.5–2 Hz		>2–3 Hz		>5–8 Hz		>8–13 Hz		>13–32 Hz							
	B	F	B	F	B	F	B	F	B	F	B	F	B	F	B	F
3	13.6	46.9	10.3	23.8	13.4	8.7	36.3	14.5	26.2	6.1	9.1	2.4	21.2	14.4	14.4	41.5
4	12.7	45.2	13.2	19.1	15.0	8.0	37.3	24.1	21.8	3.6	8.9	2.7	22.1	11.8	21.2	77.3
5	10.7	42.3	9.1	28.0	5.3	8.1	68.7	16.0	6.2	5.5	10.9	2.5	13.4	13.1	12.4	23.0
6	5.6	46.1	6.1	17.4	8.4	9.1	72.4	19.7	7.5	7.7	8.9	2.8	15.9	14.8	8.6	14.9
7	17.7	46.4	10.5	25.5	11.1	8.9	31.2	13.9	29.5	5.3	9.4	2.3	26.1	12.8	6.9	16.6
8	5.2	47.8	7.2	17.4	5.0	8.2	70.0	19.8	12.5	6.9	10.8	2.5	20.1	14.0	20.2	56.8
9	16.9	43.8	21.7	21.9	12.2	8.3	13.5	18.3	35.7	7.6	8.5	2.6	23.5	14.5	11.8	74.3
10	15.0	49.2	10.7	20.0	18.1	10.3	34.1	13.7	22.1	6.8	8.6	2.4	21.6	13.9	6.8	17.0
11	10.9	48.0	10.0	22.3	17.2	11.6	51.4	11.1	10.5	6.9	8.7	2.4	17.1	13.7	21.3	48.8
12	15.2	42.3	10.5	28.3	16.1	9.4	27.0	14.4	31.2	5.6	9.1	2.6	22.8	13.0	10.7	13.9
13	16.3	48.4	19.3	20.6	8.6	9.0	28.4	15.9	27.3	6.0	9.2	2.4	20.1	13.4	34.4	36.6
Mean	12.5	46.0	11.8	22.1	11.7	9.1	43.4	16.9	20.4	6.1	9.3	2.5	20.3	13.5	15.4	37.9
±SD	4.5	2.5	5.0	4.1	4.8	1.1	20.1	3.8	10.6	1.2	0.9	0.2	3.8	0.9	8.8	24.8

would predict the subject to be very lightly anesthetized. The presented data, however, do not support this point of view. The time course of median EEG frequency during recovery (fig. 4) and its relationship to clinical endpoints (table 1) do not suggest a steep slope in the concentration-response curve that could explain the rather rapid onset of EEG arousal observed in the first two volunteers.

A basic assumption underlying the pharmacokinetic-pharmacodynamic models currently discussed in the anesthetic literature is time invariance of the model. The state variables of the system described by the model are assumed to be independent of time, as expressed by model parameters explicitly independent of time. Although natural sleep can produce EEG patterns rather similar to those occurring during anesthesia, natural sleep is characterized by an ability to wake up spontaneously. Therefore, for the first two subjects, the pharmacologically induced state of anesthesia may have shifted towards a state similar to natural sleep during periods of zero infusion and constant low median EEG frequency.

Another important variable is the choice of the EEG parameter used for control. The original work of Bickford[12] used integrated power of the EEG for control. Later work by Bickford *et al.*[13]‡ and Bellville *et al.*[14,15] found a better control when using frequency discrimination. Rampil *et al.*[28] used spectral edge frequency (SEF) as defined by the highest frequency component of the EEG visible in the current spectrum for computerized EEG analysis during carotid endarterectomy. Homer and Stanski[17] and Scott *et al.*[10] quantitated spectral edge frequency as the 95% quantile of the EEG power spectrum, for modeling the action of thiopental, fentanyl, and alfentanil. In a more recent investigation with etomidate, Arden *et al.*[11] found median EEG frequency[8] to be a better measure of the effects of etomidate on the EEG. Spectral edge delineates the upper 5% of EEG activity.[7] Thus, it can remain stable if 5% or more of EEG activity of high frequency (>13 Hz) remains without reflecting considerable shifts of activity from the alpha band (8–13 Hz) to low frequency bands. This was true for volunteers 5 and 6. Both exhibited an almost purely alpha-type EEG having a small amount (6–7%) of beta activity. During administration of methohexital, fractional power of beta activity remained nearly stable. Thus, using spectral edge can hide the shift of EEG activity from alpha-band to low frequency bands.

In summary, we demonstrated the applicability of model-based adaptive feedback control (using quantitative EEG analysis) to methohexital-induced anesthesia. We attribute the success of feedback control to the use of the pharmacologic model and its adaptation. The feedback system does not solve the entire problem of dosing, but corrects only the dosage scheme derived from the pharmacologic model and its mean model parameters. This scheme of methohexital administration may also be a solution to the problem of EEG artifact, which may persist for some time during electrocautery. Under these circumstances, feedback control can switch to the open-loop mode. In that mode, drug delivery is determined by the pharmacokinetic-dynamic model on the basis of model parameters adjusted to the individual ones by the adaptation algorithm. If high frequency or other disturbances cease, the system returns to the closed-loop mode.

Appendix

The BET Infusion Scheme for Obtaining Constant Concentrations of a Drug

If a drug obeys linear pharmacokinetics, the superimposition principle establishes the following relationship between the drug input function, I(t); its disposition function, G(t); and the resulting concentration, c(t):

$$c(t) = \int_0^t dt' G(t - t') I(t') \qquad (A1)$$

Given the function G(t) and prescribing any desired time course of concentration c(t), equation A1 can be solved for the drug input function, I(t).

If G(t) is given by a biexponential function:

$$G(t) = Ae^{-\alpha t} + Be^{-\beta t}, \qquad (A2)$$

and c(t) is set to be the constant concentration c_1, I(t) is as follows:[25]

$$I(t) = V_1 c_1 (\delta(t) + k_{el} + k_{12} e^{-k_{21} t}), \qquad (A3)$$

where V_1, k_{el}, k_{12}, and k_{21} are given by $V_1 = 1/(A + B)$; $k_{el} = (A + B)/(A/\alpha + B/\beta)$; $k_{21} = \alpha\beta/k_{el}$; $k_{12} = \alpha + \beta - k_{el} - k_{21}$.

The symbol $\delta(t)$ denotes a bolus of unit dose at time t = 0. If equation A2 is interpreted in terms of an open mammillary two-compartment model having a central volume of distribution V_1, an elimination rate constant k_{el}, and transfer rate constants k_{12} and k_{21}, equation A3 has an immediate simple interpretation.

First, to establish a desired concentration (c_1) in a volume of distribution (V_1), one has to administer an initial bolus, $V_1 c_1$.

Second, to maintain this concentration for the subsequent period of time, one has to substitute the amount of drug removed from V_1. One has to substitute the constant amount of drug eliminated per unit time ($V_1 c_1 k_{el}$).

Third, one also has to substitute the net amount of drug transferred from the central volume of distribution to the peripheral compartment. Because this compartment equilibrates with the central compartment with time, the rate of transfer declines exponentially, $V_1 c_1 k_{12} e^{-k21t}$.

Adaptation Algorithm

The entire pharmacokinetic-dynamic model used in this study is determined by a set of eight parameters (A, α, B, β, E_0, E_{max}, c_0, and γ). Relating the drug input function I(t) directly

to drug effect E by inserting c(t) of equation A1 into the pharmacodynamic equation,

$$E = E_0 - E_{max} \frac{c^\gamma(t)}{c_0^\gamma + c^\gamma(t)}$$

$$= E_0 - E_{max} \frac{(c(t)/c_0)^\gamma}{1 + (c(t)/c_0)^\gamma}, \quad \text{(A4)}$$

one observes that this relationship depends only on seven parameters (A/c_0, α, B/c_0, β, E_0, E_{max}, and γ). This is due to the scale invariance of formula A4 under the scale transformation $(c_0, c) \rightarrow (\lambda c_0, \lambda c)$ for any number $\lambda \neq 0$.

A full adaptation algorithm requires an updating of all seven parameters. To get a confident estimation of all parameters, one must choose an experimental setup, such that the signal output is sensitive to all parameters, *i.e.*, wide varying concentrations and wide varying effects between baseline and maximum. This study has had, however, the exact opposite aim—that is, to establish a constant effect. Therefore, it is advisable to update only a minimal set of parameters necessary to adjust for the individual. We chose to estimate and update A and B, and to fix all other parameters. This set allows us to adjust for the subject's response to a bolus (short-term adjustment) and to a constant-rate infusion at steady-state (long-term adjustment). Immediately after bolus injection D, the concentration of drug is $c_D = D(A + B)$; whereas, during constant-rate infusion I_{ss}, the concentration is $c_{ss} = I_{ss}(A/\alpha + B/\beta)$. The effect E may be regarded as a function of A and B and the drug input I(t):

$$E = E(A, B, I(t))$$

Denoting by $A + \delta A$ and $B + \delta B$ the true microconstants for an individual subject, the difference between measured and predicted concentration (ΔE) can be expanded in a Taylor series, as follows:

$$\Delta E = E(A + \delta A, B + \delta B, I(t)) - E(A, B, I(t))$$

$$= (\partial E/\partial A)\delta A + (\partial E/\partial B)\delta B + \cdots \quad \text{(A5)}$$

In conjunction with the condition to minimize the expression $\delta A^2 + \delta B^2$, equation A5 was used to solve for δA and δB. From the updated values, new microconstants were calculated that served to correct the drug input function.

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