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Effective Therapeutic Infusions Produced by Closed-Loop Feedback Control of Methohexital Administration during Total Intravenous Anesthesia with Fentanyl

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A combined pharmacokinetic and pharmacodynamic model of methohexital was used to establish and evaluate feedback control of methohexital delivery during total intravenous anesthesia with fentanyl in 11 surgical patients. The median frequency of the EEG power spectrum served as the pharmacodynamic variable constituting feedback. Based on previous investigations a median frequency from 2–3 Hz was chosen as the desired EEG set point. In addition to methohexital, patients were given a 10-min loading infusion of 0.5 mg of fentanyl followed by a constant-rate infusion of 0.22 mg/h. In agreement with an earlier similar study in volunteers given only methohexital and aiming at the same set point, identical distribution of EEG power was achieved in the current study. The decrease of median EEG frequency to 2–3 Hz was primarily induced by an increase in fractional power in the 0.5–2- Hz frequency band to 46 ± 4%. The average requirement of methohexital during the first 2 h was 675 ± 250 mg. The authors conclude that model-based feedback control of intravenous methohexital delivery can help establish and quantitate methohexital requirements during total intravenous anesthesia with fentanyl. (Key words: Anesthesia techniques: total intravenous. Anesthetics, intravenous: methohexital. Monitoring: electroencephalography. Pharmacodynamics: depth of anesthesia. Pharmacokinetics: adaptive feedback control.)

THE ELECTROENCEPHALOGRAM (EEG) has been shown to be sensitive to the administration of hypnotic agents. Some EEG derivations such as spectral edge frequency[1–3] or median EEG frequency[4–7] have been used to quantitate shifts in EEG frequency that are associated with administration of drugs. Specifically, both measures decrease as drug concentration and depth of anesthesia increases. We recently used this relationship to establish closed-loop feedback control of methohexital administration in volunteers.[7] The algorithm governing feedback control uses a combined pharmacokinetic-pharmacodynamic model[8,9] of the relationship between drug input and effect[5] to determine the dosing of methohexital based on measured EEG frequency and the desired set point. That is, previous investigation has shown that frequencies in the range of 2–3 Hz indicate a level of anesthesia sufficient to ensure unconsciousness.[7]

Such a method of drug administration may solve several problems associated with anesthetic drug therapy. Because feedback control minimizes the problem of interindividual variability in drug disposition and pharmacodynamic response, it helps the anesthesiologist in titrating the dose to patient need. Moreover, feedback control based on EEG analysis can be used to establish and study precisely dose requirement curves[10] on objective and quantitative grounds. Applying this method clinically to drug combinations, one is able to quantitate interactions between drugs at stable pharmacodynamic effects without the need to exceed or fall below the therapeutic range. Hence, feedback control of drug delivery might be suited to investigate uncommon or new anesthesia techniques such as total intravenous anesthesia.

Although opioids such as fentanyl or alfentanil do have hypnotic potential, the use of such agents by themselves to produce both analgesia and sleep is not considered desirable for general surgery. The consensus is that the combination of a hypnotic agent and an opioid is a more effective way of providing analgesia and amnesia during total intravenous anesthesia.

On the other hand, the repetitive dosing of short-acting induction agents is an unsafe and inconvenient way of preventing intraoperative awareness and postoperative recall, especially when neuromuscular blockade is in effect. Although the continuous administration of hypnotic compounds produces a smoother time course of blood concentration and thus a smoother effect, the problem of ensuring the adequacy of anesthesia remains unless drug effect can be measured and controlled.

The present study investigates the applicability of automatic feedback control of methohexital administration in the clinical setting of total intravenous anesthesia with fentanyl, methohexital, oxygen, and air.

Methods and Materials

SUBJECTS AND PROTOCOL

We obtained informed written consent and institutional approval to study 11 patients (18–55 yr) undergoing general surgery. Preanesthetic medication consisted of oral administration of 1 mg of flunitrazepam 45 min before anesthesia. In some instances, 1 mg of flunitrazepam was given the night before surgery. Five minutes before tra-

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cheal intubation, a loading infusion of 0.5 mg of fentanyl was given over 10 min, followed by a maintenance infusion of 0.22 mg/h. If cardiovascular signs or sweating and tearing indicated insufficient antinociception, a 0.1 mg bolus of fentanyl was given and the infusion rate was increased by 20%. We induced anesthesia with 80 mg of methohexital and facilitated endotracheal intubation with 80 mg of succinylcholine. Clinical monitoring consisted of an electrocardiogram, noninvasive automatic determination of blood pressure every 3 min (Dinamap®, Critikon), and measurement of end-tidal concentrations of CO_2 (Hewlett-Packard Monitor). Artificial ventilation was adjusted to keep end-tidal P_{CO_2} at 35 mmHg. Just before skin incision, feedback control of methohexital delivery was activated.

EEG Analysis

Four leads (C_z-F_i and 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. 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, divided 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 algorithms, from which the median EEG frequency (50% quantile) of the power spectrum was derived. In addition, fractional power in the frequency bands 0.5–2 Hz, >2–5 Hz, >5–8 Hz, >8–13 Hz, >13–32 Hz, and mean amplitude were calculated and displayed on the text screen.

Administration Device and Algorithm

An infusion pump (IP 4®, Vickers) was attached to the portable computer (Eurocom®, Eltec) 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 to less than 20 mg/min. The solution was administered through a central venous catheter or through an indwelling catheter inserted in a forearm vein. A linear model described by a biexponential disposition function c(t) after iv bolus administration was assumed to represent a valid pharmacokinetic model:

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

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

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

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. Initial parameters were chosen as described elsewhere.[7] Specifically the interval of 2–3 Hz was chosen as the desired EEG level (set point).

If the median EEG value was 2–3 Hz, the computer used an infusion scheme[7,11] to maintain the current methohexital concentration and, thus, effect, as predicted by the pharmacokinetic model on the basis of the updated model parameters. If the median EEG value fell outside this range, the computer used the difference between measured and predicted values (ΔE) to correct model parameters. The updated values were then 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. If a burst-suppression pattern occurred, the rate of infusion was set to zero; if artifacts were detected, the rate of infusion was calculated according to the updated model. This cycle was performed every EEG epoch.

Results

Figure 1 depicts the time course of median EEG frequency in a typical patient. None of the patients showed signs of being awake, nor did any patient recall any intraoperative event immediately after recovery and 1 day after surgery. Table 1 provides the length of feedback control and the amount of methohexital given (total per minute and per hour and body weight). The mean (±SD) average amount of methohexital given per minute was 5.30 ± 1.34 mg. Figure 2 depicts the cumulative amount of methohexital (mean ± SD) required for the 11 patients

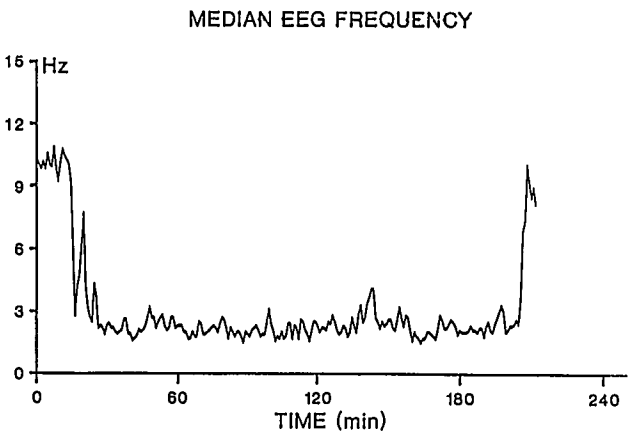

FIG. 1. The time course of median EEG frequency during feedback control of methohexital administration in a typical surgical patient. The goal of the feedback control was to keep the median EEG frequency between 2 and 3 Hz.

TABLE 1. General Patient Data and Methohexital Requirement during Feedback Control in 11 Patients Undergoing Total Intravenous Anesthesia with Fentanyl for Surgery

	General Patient Data				Methohexital		
Patient	Type of Surgery	Weight (kg)	Height (cm)	Duration (min)	Amount (mg)	Amount per time (mg/min)	Amount per time per body weight ($mg \cdot h^{-1} \cdot kg^{-1}$)
1	breast	72	162	209	1337	6.39	5.33
2	proctocolectomy	87	167	313	966	3.08	2.12
3	breast	88	168	160	1195	7.46	5.09
4	breast	65	164	124	741	5.98	5.52
5	breast	58	162	120	730	6.08	6.29
6	breast	57	160	148	556	3.76	3.96
7	hemicolectomy	74	168	182	1024	5.63	4.56
8	breast	86	168	136	785	5.77	4.03
9	breast	60	158	127	701	5.52	5.50
10	splenectomy	55	178	144	501	3.48	3.80
11	breast	62	163	138	711	5.15	4.98
	Mean	69.5	165.3	163.7	841	5.30	4.65
	SD	12.7	5.4	56.3	260	1.34	1.14

comedicated with fentanyl. To define an asymptotic steady-state infusion rate (I_{as}) we used nonlinear curve fitting to fit the following formula[10] to the mean methohexital requirement curve k_{inf}:

$$k_{inf} = D*(1 - \exp(-k*t)) + I_{as}^{*}t \quad (3)$$

The best fit was achieved with the following set of parameters: D = 88.2 mg, k = 0.289/min, and I_{as} = 4.9 mg/min. Figure 3 provides the curve for the measured requirement of methohexital for the first 2 h and the fitted line resulting from the above process. Thus, on average, an effective therapeutic infusion of 4.9 mg/min was required to maintain the therapeutic set point. Only for the first 30 min was a higher, steadily declining infusion rate necessary.

Table 2 gives hemodynamic effects at specific moments in time as well as means (±SD) of systolic and diastolic blood pressure and heart rate during the feedback period.

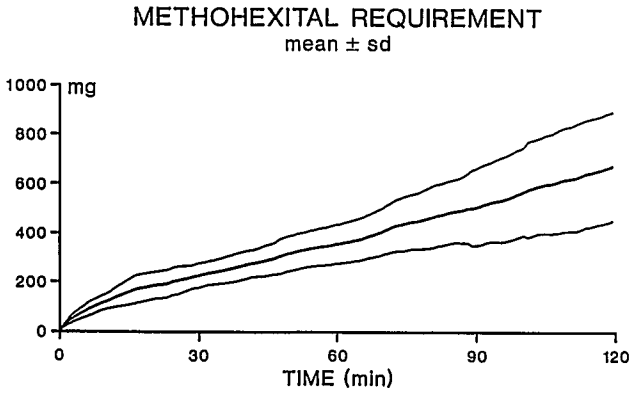

FIG. 2. Shown is the mean (±SD) cumulative dose of methohexital required to keep the median EEG frequency between 2 and 3 Hz during total intravenous anesthesia with fentanyl in 11 surgical patients.

The indicated recovery time denotes the period from cessation of both methohexital and fentanyl administration to response to verbal commands. In patient number 2, fentanyl infusion was increased by 20% preceded by a bolus of 0.1 mg when heart rate and diastolic blood pressure increased simultaneously above 100 beats per min and 100 mmHg, respectively.

Table 3 provides values for fractional EEG power in the indicated EEG frequency bands, the median EEG frequency, and mean amplitude observed during the feedback control period of methohexital administration. There was no significant linear correlation between the average rate of methohexital administration and body weight or height, heart rate, or blood pressure.

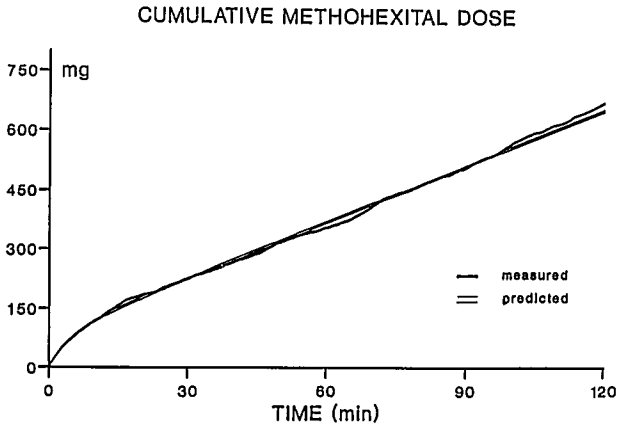

FIG. 3. The curve for the mean cumulative dose requirements of methohexital in 11 surgical patients is compared with the best-fit prediction of formula (3) in the text. The prediction indicates that an effective theapeutic infusion (ETI) of methohexital, as guided by continuous analysis of EEG median frequency, would consist of administration of 4.9 mg of the drug per min.

TABLE 2. Hemodynamic Effects during and Recovery Time from Anesthesia by Feedback-Controlled Methohexital Administration in 11 Patients Undergoing Total Intravenous Anesthesia with Fentanyl for Surgery

Patient	Blood Pressure (mmHg)					Diastolic	Systolic	Heart Rate (l/min)	Recovery Time (min)
	Baseline	Intubation	Skin incision	Skin closure	Extubation				
1	170/105	145/100	140/110	100/75	135/85	97 ± 12	136 ± 16	91 ± 7	26
2	140/80	140/85	140/90	120/80	150/95	86 ± 11	134 ± 18	92 ± 9	10
3	130/75	160/90	125/80	130/90	140/80	83 ± 8	125 ± 13	83 ± 7	15
4	135/85	130/80	140/90	140/90	170/95	80 ± 11	127 ± 15	65 ± 7	21
5	125/75	120/80	110/80	100/70	130/80	70 ± 8	108 ± 12	94 ± 8	24
6	110/80	120/80	105/60	95/70	130/80	74 ± 6	105 ± 6	73 ± 3	31
7	135/90	140/70	120/80	125/80	135/90	84 ± 7	129 ± 8	95 ± 8	4
8	140/85	160/100	110/70	120/75	190/100	76 ± 8	123 ± 12	59 ± 5	30
9	125/75	135/85	110/80	90/50	120/75	78 ± 12	113 ± 15	81 ± 7	12
10	120/70	125/80	105/60	115/90	120/75	78 ± 8	125 ± 10	104 ± 13	15
11	135/80	140/100	115/85	110/75	145/95	81 ± 10	126 ± 9	76 ± 9	19

* Mean ± SD during feedback control.

Discussion

The present study demonstrates the applicability of a recently described feedback controller (based on median EEG frequency) for methohexital administration during total intravenous anesthesia with fentanyl, oxygen, and air.

The pattern of EEG power distribution achieved in the present study was identical to that in our earlier, similar study on volunteers.[7] However, although surgical stimulation was certainly stronger than the pinprick and other stimuli given to volunteers, the methohexital requirement was significantly less (*i.e.*, one-third less) in the surgical patients (676 ± 250 mg) for the first 2 h than in the volunteers (1,020 ± 160 mg).

Fentanyl induces EEG slowing at moderate to high doses. After a bolus dose of 0.5 mg, EEG slowing lasts for only approximately 10 min as indicated by early findings of Kubicki.[12] Even if the loading dose is followed as in this study by a maintenance dose of 0.22 mg/h EEG slowing reverses to near normal values. Figure 4 compares as an example three raw EEG traces obtained at different conditions for patient number 2. Trace 1 was recorded prior to anesthesia but after preanesthetic medication with flunitrazepam and corresponds to a median EEG frequency of 9.2 Hz. The second trace, recorded 20 min after commencement of fentanyl maintenance infusion, corresponds to a median EEG frequency of 8.3 Hz. The bottom trace associated with median EEG frequency of 2.6 Hz was recorded after institution of feedback control with methohexital.

The main reason for the reduction in dose requirement of methohexital was presumably the addition of fentanyl, although one cannot eliminate the possibility that preanesthetic medication with flunitrazepam also contributed. Although our current study does not allow one to distinguish the contribution of flunitrazepam from that of fentanyl regarding dose reduction of methohexital, it does indicate the value of feedback-controlled drug delivery systems in studying and quantitating interactions

TABLE 3. Fractional EEG Power, Median EEG Frequency, and Mean Amplitude during Feedback Control of Methohexital Delivery

Patient	Fractional EEG Power					Median (Hz)	Mean Amplitude (μV)
	0.5–2	>2–5	>5–8	>8–13	>13–32		
1	0.47	0.16	0.12	0.18	0.07	2.6	14.4
2	0.49	0.20	0.10	0.16	0.05	2.2	10.6
3	0.39	0.22	0.13	0.18	0.09	3.1	20.0
4	0.42	0.15	0.15	0.21	0.06	2.3	17.2
5	0.48	0.21	0.08	0.17	0.06	2.2	39.7
6	0.50	0.20	0.06	0.19	0.05	2.1	36.2
7	0.46	0.19	0.07	0.19	0.09	2.5	21.2
8	0.45	0.17	0.10	0.20	0.08	2.6	19.4
9	0.42	0.18	0.13	0.18	0.09	2.9	37.6
10	0.51	0.17	0.05	0.18	0.09	2.1	37.0
11	0.48	0.19	0.08	0.17	0.08	2.4	28.3
Mean	0.46	0.19	0.10	0.18	0.07	2.46	25.3
SD	0.04	0.02	0.03	0.02	0.02	0.34	11.0

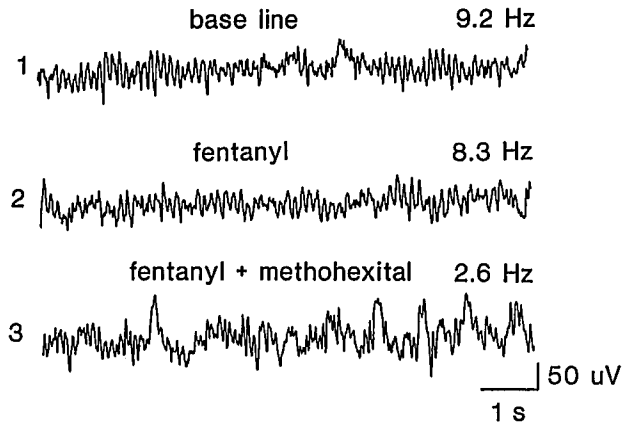

FIG. 4. Fentanyl given as a steady-state infusion of 0.22 mg/h has only little influence on the frequency content of the raw EEG (trace 2). It decreases median EEG frequency from baseline values of 9.2 Hz (trace 1) to 8.3 Hz. The addition of methohexital decreased EEG frequency more pronounced as indicated by trace 3. Traces 1 to 3 were recorded in one patient as baseline conditions, during fentanyl administration, and during the feedback period with methohexital.

between drugs, an idea proposed by Bellville *et al.*[13] in 1960.

As in an earlier, similar study on volunteers,[7] we chose in this study as set point an EEG level of 2–3 Hz of median EEG frequency. The rationale for this choice was the proven efficacy of methohexital in maintaining nonresponsiveness to random stimulation in volunteers given this set point. One cannot exclude the possibility that a higher set point, *e.g.*, 4–5 Hz, for the combined administration of fentanyl and methohexital in surgical patients could have been an equally reasonable choice. The observed clinical signs in this study, however, like blood pressure, heart rate, or recovery time do not indicate an unreasonably deep level of anesthesia. The identification of the optimal EEG set point in terms of maximal hemodynamic stability, simultaneously minimal recovery time, and likelihood of intraoperative awareness needs further investigations.

Beside more scientifically based considerations, one outstanding question remains: Does any clinically relevant benefit occur to the patient or anesthesiologist by using a feedback-controlled intravenous drug delivery system rather than the conventional intermittent bolus technique? Because controlled clinical studies comparing these methods do not exist, this question cannot be answered on the basis of outcome studies. However, there are a number of reasons to anticipate a benefit with feedback control of drug administration. Ausems *et al.*[14] recently showed that open-loop controlled interactive strategies for infusion of alfentanil produced a more stable hemodynamic state than did conventional bolus administration. Therefore, continuous administration of hypnotic agents based on continuous EEG analysis may produce a more stable hypnotic effect than intermittent bolus administration guided by clinical signs.

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