40 Hz Auditory steady-state response and EEG spectral edge frequency during sufentanil anaesthesia

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Purpose: The auditory steady-state evoked response (ASSR) is an evoked potential which provides a sensitive measure of the effects of general anaesthetics on the brain. We used pharmacokinetic-pharmacodynamic (PK-PD) modelling to compare the effects of sufentanil on the amplitude of the ASSR with its effect on spectral edge frequency (SEF) of the electroencephalogram.

Methods: Nine patients scheduled for elective cardiac surgery participated. Midazolam ($70 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{im}$) was given 60 min before entering the operating room. Anaesthesia was induced with $5 \mu\text{g}\cdot\text{kg}^{-1}$ sufentanil at a rate of $0.83 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The ASSR, SEF and plasma sufentanil concentrations were measured for 30 min after induction of anaesthesia before surgery. The half-life between the central and effect site compartments ($t_{1/2}K_{eo}$), the 50% inhibitory concentration (IC_{50}) and the slope factor (γ) were computed.

Results: The amplitude of the ASSR increased during the first three minutes of infusion of sufentanil by up to 40%. This was followed by a rapid decrease between the fourth and fifth minutes to 16% of baseline. The SEF decreased progressively during the first five minutes of infusion to 18% of baseline. Both measures subsequently showed modest recovery. The parameters γ , IC_{50} and $t_{1/2}K_{eo}$ for ASSR were (mean $\pm$ SD) 6.0 ± 3.7 , $2.1 \pm 1.2 \text{ ng}\cdot\text{ml}^{-1}$ and $7.3 \pm 2.4 \text{ min}$. For SEF the values were 5.9 ± 5.2 , $1.4 \pm 0.7 \text{ ng}\cdot\text{ml}^{-1}$ ($P < 0.05$ compared with ASSR) and $6.8 \pm 2.4 \text{ min}$.

Conclusion: The sensitivity of ASSR to sufentanil is less than that of the SEF.

Objectif : La réponse auditive soutenue (RAS) est un potentiel évoqué auditif qui constitue une mesure très sensible des effets des anesthésiques généraux sur le cerveau. Nous avons utilisé un modèle pharmacocinétique/pharmacodynamique pour comparer les effets du sufentanil sur l'amplitude de la RAS avec ses effets sur la fréquence de puissance quantile 95% (F95) de l'électroencéphalogramme.

Méthodes : Neuf patients devant subir une chirurgie cardiaque programmée ont participé à l'étude. Du midazolam ($70 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{im}$) a été administré une heure avant l'entrée en salle d'opération. Nous avons induit l'anesthésie avec une perfusion de sufentanil ($5 \mu\text{g}\cdot\text{kg}^{-1}$) à un débit de $0.83 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Avant le début de la chirurgie, nous avons mesuré la RAS, F95 et la concentration plasmatique de sufentanil à plusieurs reprises pendant 30 minutes. Nous avons calculé la demi-vie de transfert entre le compartiment central et le compartiment effecteur ($t_{1/2}K_{eo}$), la concentration inhibitrice 50% (CI_{50}) ainsi que la pente (γ) de la courbe concentration-réponse.

Résultats : L'amplitude de la RAS a augmenté de 40% pendant les trois premières minutes de la perfusion de sufentanil pour ensuite chuter de façon abrupte lors des deux minutes subséquentes et atteindre 16% du niveau de base. La F95 a diminué de manière progressive durant les cinq premières minutes de la perfusion pour atteindre 18% du niveau de base. Les deux mesures ont par la suite augmenté de façon modeste. Les paramètres γ , CI_{50} et $T_{1/2}K_{eo}$ pour la RAS étaient (moyenne $\pm$ écart type) 6.0 ± 3.7 , $2.1 \pm 1.2 \text{ mg}\cdot\text{ml}^{-1}$ et $7.3 \pm 2.4 \text{ min}$. Pour la F95, les valeurs étaient 5.9 ± 5.2 , $1.4 \pm 0.7 \text{ mg}\cdot\text{ml}^{-1}$ ($P < 0.05$ en comparaison avec la RAS) et $6.8 \pm 2.4 \text{ min}$.

Conclusion : La RAS est une mesure moins sensible que la F95 pour évaluer les effets du sufentanil sur le cerveau.

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Accepted for publication November 16, 1997.

THE auditory steady-state response (ASSR) is a sustained electrical response of the brain to rapidly presented auditory stimuli. It appears when the rate of stimulus delivery is sufficiently rapid to produce overlapping of the responses to individual stimuli. Because the ASSR is usually largest for stimulus rates near 40 Hz the label 40 Hz ASSR is frequently used.¹ The amplitude of the ASSR is drastically reduced by anaesthetic agents. This attenuation may reflect loss of consciousness.² In a previous study,³ we have shown that sufentanil profoundly attenuates the amplitude of the ASSR. Following 5 $\mu\text{g}\cdot\text{kg}^{-1}$ sufentanil given over three to five minutes for induction of anaesthesia, the 40 Hz ASSR amplitude decreased to 16% of baseline concurrently with loss of consciousness.³ The attenuation of the ASSR seemed to occur more abruptly than the progressive reduction by sufentanil of the spectral edge frequency (SEF) of the electroencephalogram (EEG).⁴ Spectral edge frequency is the most widely used measure of the effects of opioids on the brain, including sufentanil.⁵ The different time course for the changes of the ASSR and the SEF could, perhaps, be explained by different doses and rates of administration. Nevertheless, the possibility that the effects of sufentanil on the ASSR and SEF would follow a different time course was interesting and deserved inquiry. The purpose of this investigation was to compare the effects of sufentanil on the 40 Hz ASSR and the SEF recorded simultaneously in the same patients. The arterial serum concentration of sufentanil was measured to conduct pharmacokinetic-pharmacodynamic (PK-PD) modelling⁶⁻⁷ to identify the cause(s) for differences in time course of sufentanil effect between the ASSR and SEF. Possible causes are differences in sensitivity to sufentanil, in the slope of the concentration effect curve or in the blood-effect compartment equilibration rate constant.

Methods

Patients

After institutional Ethics Committee approval and written informed consent, we studied ten ASA III patients scheduled for elective aortocoronary bypass grafting. They had no history of neurological or otological disease. Nine patients (eight men; mean age, 54.6 $\pm$ (SD) 7.5 yr) completed the study. The data from the remaining patient were excluded because of artifacts.

The patients were interviewed postoperatively to inquire about recall of intraoperative awareness. The questions were: 1) describe the events which occurred before your surgery from the time you left your room to as far as you can remember, 2) describe the events which occurred after your operation starting as early as you can remember, 3) do you recall events which

could have occurred during surgery? 4) describe your recent dreams or nightmares.

Anaesthetic technique

In addition to their routine nitrate, beta blocker and calcium channel blocker medication, patients received 0.07 $\text{mg}\cdot\text{kg}^{-1}$ midazolam in 60 min before entering the operating theatre. After placement of the electrocardiographic electrodes and the pulse oximeter, peripheral venous and radial arterial catheters were inserted under local anaesthesia. After administration of 0.02 $\text{ml}\cdot\text{kg}^{-1}$ of a pancuronium and vecuronium mixture (0.2 $\text{mg}\cdot\text{ml}^{-1}$ pancuronium and 0.8 $\text{mg}\cdot\text{ml}^{-1}$ vecuronium), anaesthesia was induced with 5 $\mu\text{g}\cdot\text{kg}^{-1}$ sufentanil infused at constant rate over six minutes with an infusion pump. The level of consciousness, determined by responsiveness to verbal command ("open your eyes"), was assessed every minute. After loss of consciousness, 0.08 $\text{ml}\cdot\text{kg}^{-1}$ pancuronium-vecuronium mixture was given to facilitate tracheal intubation. The lungs were ventilated mechanically with air and oxygen ($\text{FiO}_2 = 0.4$) to keep $\text{P}_{\text{ET}}\text{CO}_2$ at 30–35 mmHg. No inhaled anaesthetics were used. A pulmonary artery catheter was then inserted. After the 30 minute recording period, anaesthetic management proceeded without restriction.

Auditory steady-state responses (ASSR)

An IBM-compatible computer with two analog-to-digital (A/D) and digital-to-analog (D/A) conversion cards was used for stimulus generation and signal acquisition.

STIMULI

Tonebursts (500 Hz, 10 msec duration, 2 msec rise/fall time, 84 dB peak equivalent sound pressure level) were presented binaurally at a rate of 40 per second via insert earphones (Etymotic Research, model ER3A).

RECORDING

The EEG was recorded with gold-plated cup electrodes attached with saline gel and collodion. Inter electrode impedances were less than 3 k Ω (30 Hz). Three electrodes were placed according to the International 10–20 system at frontal (AFz) and central (Cz) mid-sagittal scalp locations, with reference to the right mastoid (M2).⁸ The amplification band-pass was from 0.3 to 100 Hz (Grass Model 12A5 amplifier).

The epoch lasted 3.425 msec, with a sampling frequency of 298.98 Hz per channel and a resolution of 12 bits (1024 data points). The interval between onset of successive epochs was one minute. Epochs contaminated by artifacts were rejected. The rejection level was $\pm 200 \mu\text{V}$. Epochs were averaged on-line in groups of 10. Recordings were obtained every minute starting two

minutes before to thirty minutes after the start of the sufentanil infusion.

MEASUREMENTS

After computing the amplitude spectrum of the averaged unfiltered traces using fast Fourier transformation,⁹ the amplitude and phase at 40 Hz ASSR were recorded. The mean amplitude between 35–39 Hz and 41–45 Hz was computed from the spectrum to estimate residual background noise.

Electroencephalogram

Because averaging uniformly attenuates all frequencies, it is possible to estimate the EEG from averaged traces.¹⁰ After computing the power spectrum of the unfiltered averaged traces, we measured the SEF, defined as the frequency below which 95% of the power between 0.5 and 30 Hz occurs.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation (SD). The differences between recording periods were analysed by one-way analysis of variance (ANOVA) for repeated measures, using the Geisser-Greenhouse adjustment of the significance levels.¹¹ Tukey's HSD¹¹ test was used for *post-hoc* comparisons. Pearson's product-moment correlation coefficient and paired *t* tests were also used.¹² Criteria for significance was $P < 0.05$.

Serum sufentanil concentration

ASSAY

Duplicate 5 ml arterial blood samples were drawn at the following times: pre-induction, and at 2, 4, 6, 8, 10, 15, 20, 25 and 30 min after the start of this sufentanil infusion. Each sample was allowed to clot and was centrifuged. The serum was separated, pooled and frozen at -20°C . Serum sufentanil concentrations were determined in duplicate using a radioimmunoassay kit (Janssen Pharmaceutica, Mississauga, Ontario).¹³ The sensitivity was $1 \text{ ng}\cdot\text{ml}^{-1}$. The mean coefficient of variation intra- and inter- assay was 5.1 and 6.2%, respectively.

PHARMACODYNAMIC MODELLING

Pharmacodynamic modelling was performed using the program SIPHAR© (Simed, Créteil, France).⁶ For each patient, the plasma sufentanil concentrations were fitted to an open two compartment model with a constant input rate. The ASSR and SEF values were fitted every minute for the first ten minutes following the start of the sufentanil infusion. From 11 to 30 min, the values were averaged over five min (from two min before to two min after the blood sample) to match the rate of blood sampling. A non-parametric link model⁶ was used

to collapse the hysteresis. The model incorporates an effect compartment to characterise the time lag between changes in serum drug concentration and drug effect. K_{eo} is the rate constant for transfer from the central compartment and the effect compartment. The corresponding half-life is $t_{1/2}K_{eo}$.

Sigmoid $E_{\max}$ modelling of the effect compartment concentration was carried out to obtain the IC_{50} and gamma values according to the following equation:⁷

$$A(t) = E_0 - E_{\max} \cdot C_e(t)^g / [IC_{50}^g + C_e(t)^g]$$

where $A(t)$ is the ASSR amplitude or SEF at time t ; E_0 is the pre-infusion, baseline value; $E_{\max}$ is the maximal decrease caused by sufentanil; IC_{50} is the effect-compartment concentration of sufentanil ($\text{ng}\cdot\text{ml}^{-1}$) that produces 50% of the maximal decrease; g (gamma) is a dimensionless parameter of sigmoidicity curve steepness; and $C_e(t)$ is the predicted sufentanil concentration ($\text{ng}\cdot\text{ml}^{-1}$) in the effect compartment. Modelling can be performed either by using the actual measured baseline values (fixed E_0) or by parametrically adjusting the baseline (derived E_0). In this study, we adopted the fixed E_0 method as our standard. E_0 was chosen as the highest of the values obtained at times -2, -1 and 0 min relative to the start of the infusion. Results obtained with the derived E_0 method are included for completeness.

Results

All patients had an uneventful postoperative recovery and denied conscious recall of intraoperative events. Loss of consciousness as determined by loss of response to verbal command occurred at a range of 2.5 to 5.5 (mean 3.1) min from the start of the sufentanil infusion. It was difficult to determine with confidence the time when consciousness was lost. Muscle rigidity, upward eye deviation and repetitive fine hand movements (similar to those seen in extrapyramidal disorders) frequently occurred during induction and interfered with the evaluation of consciousness.

ASSR

The amplitude data are shown in Table I. The effect of time and of recording site (AFz vs Cz) were analysed with ANOVAs for repeated measures. The effect for time was highly significant ($P < 0.001$). There was an amplitude increase during the first three minutes of infusion. This was followed by a very rapid decrease between the fourth and fifth minute after the start of the sufentanil infusion. Amplitude was larger ($P < 0.025$) at Cz than at AFz (0.11 vs $0.08 \mu\text{V}$ across all periods). There also was a site-time interaction ($P < 0.002$), indicating that the absolute amplitude difference between sites was larger during the baseline recordings than afterwards.

TABLE I mean $\pm$ standard deviation

Time (min)	ASSR amplitude (μ V)		SEF (Hz)	
	AFz	Cz	AFz	Cz
Baseline	0.23 $\pm$ 0.15	0.27 $\pm$ 0.14	18.8 $\pm$ 5.9	22.8 $\pm$ 1.9
0	0.28 $\pm$ 0.16	0.34 $\pm$ 0.18	20.1 $\pm$ 5.6	23.6 $\pm$ 3.0
2	0.31 $\pm$ 0.20	0.36 $\pm$ 0.22	13.7 $\pm$ 5.4	15.7 $\pm$ 5.4
4	0.05 $\pm$ 0.05	0.08 $\pm$ 0.06	4.5 $\pm$ 1.3	5.8 $\pm$ 2.1
6	0.04 $\pm$ 0.03	0.05 $\pm$ 0.07	4.8 $\pm$ 1.3	5.8 $\pm$ 1.0
8	0.04 $\pm$ 0.02	0.04 $\pm$ 0.03	3.6 $\pm$ 0.7	4.4 $\pm$ 1.7
10	0.03 $\pm$ 0.03	0.04 $\pm$ 0.04	3.7 $\pm$ 0.9	4.1 $\pm$ 1.0
15	0.04 $\pm$ 0.02	0.05 $\pm$ 0.05	4.1 $\pm$ 1.1	5.5 $\pm$ 2.4
20	0.03 $\pm$ 0.03	0.05 $\pm$ 0.04	4.1 $\pm$ 0.9	5.8 $\pm$ 1.4
25	0.05 $\pm$ 0.05	0.06 $\pm$ 0.04	4.5 $\pm$ 1.3	5.6 $\pm$ 1.6
30	0.07 $\pm$ 0.08	0.09 $\pm$ 0.09	5.4 $\pm$ 1.6	5.7 $\pm$ 2.0

TIME 0: Start of the infusion of sufentanil.
BASELINE: Mean of the recordings started at times -2 and -1 min.
To limit space, results are given only for times when blood samples were taken, although recordings were obtained every minute

The initial amplitude increase was not accompanied by a proportional increase in residual background noise. The mean noise level pooled over the 35–39 Hz and 41–45 Hz intervals was 0.06 μ V during baseline. The mean amplitude relative to baseline was 0.96, 1.14, 0.85, 0.96, 0.77 and 0.80 for the recordings started 0, 1, 2, 3, 4, and 5 min after the beginning of the infusion. Figure 1 shows the waveforms for one patient. Figure 2 shows the 40 Hz ASSR amplitude at Cz as a function of time for each patient.

SEF

The data are presented in Table I. The effect of time and of recording site (AFz vs Cz) were analysed with an ANOVA for repeated measures. The effect of time was highly significant ($P < 0.001$). The SEF decreased progressively during the first five minutes of the infusion of sufentanil. The SEF was higher ($P < 0.001$) at Cz than at AFz (8.0 vs 6.7 Hz across all periods). There also was a site-time interaction ($P < 0.003$), indicating that the absolute difference between sites was larger during baseline recordings than afterwards. However, the profile of SEF changes over time was similar for both recording sites. Figure 3 shows the SEF at Cz as a function of time for each patient.

Relationship between 40 Hz ASSR amplitude and SEF

The ASSR amplitude and SEF both reached their lowest levels within six minutes (Figure 4). The SEF decreased progressively. In contrast, the ASSR amplitude increased for the first four minutes before falling abruptly to the lowest levels. Both measures subsequently showed very modest progressive recovery. Because of the difference in the temporal profiles, the results for the first 10 min were analysed separately from those of the last 20 min.

First Part: 0–10 min. An ANOVA for repeated measures with two factors (time: 11 levels from $t = 0$ to $t = 10$ min; type of recording: two levels – 40 Hz

FIGURE 1 Amplitude spectra from a representative patient (C). Y axis: amplitude in μ V; X axis: frequency in Hz. The 40 Hz ASSR is shown by the arrow for the baseline (base) recording. Sufentanil caused a marked increase in low frequency (below 5 Hz) amplitude and a profound attenuation of the 40 Hz ASSR. Low frequency amplitude clipped to reduce vertical space.

ASSR amplitude and SEF) yielded a highly significant effect of time ($P < 0.001$) and interaction ($P < 0.001$), confirming that the temporal profile was not the same for the two types of recording.

Second Part: 11–30 min. An ANOVA as above (except that the number of levels for time was 20) yielded an effect of time ($P < 0.05$), confirming a modest recovery. No other effect approached significance.

FIGURE 2 40 Hz ASSR amplitude at Cz from -2 to 30 min after the beginning of the infusion of sufentanil for each patient.

FIGURE 3 SEF at Cz from -2 to 30 min after the beginning of the infusion of sufentanil for each patient.

We examined the results from baseline to six minutes after infusion for correlation between ASSR amplitude and SEF in individual patients. This period

FIGURE 4 Changes of the ASSR amplitude (full line) and of the SEF (dotted line) relative to baseline. Mean values $\pm$ SEM.

was chosen because the most pronounced changes occurred during that period. Six patients showed a correlation ($P < 0.01$; Pearson's $R > 0.83$) between the ASSR amplitude and SEF. The three patients who did not show a correlation are those who showed the most pronounced increase in the amplitude of the ASSR during induction.

There was no correlation between the ASSR amplitude and SEF across patients during baseline or at any subsequent recordings. The patients who, during a given period, had the large ASSR amplitude did not necessarily have the large (or small) SEF.

Sufentanil assay and pharmacodynamics

Figure 5 shows the sufentanil serum concentration time curves for each patient. Pharmacokinetic-pharmacodynamic modelling revealed a difference in sensitivity between the 40 Hz ASSR and SEF. The mean IC_{50} for the ASSR was higher than for the SEF (2.1 ± 1.2 vs 1.4 ± 0.7 ng·ml⁻¹; $P < 0.05$) (Table II). This indicates that for a comparable attenuation (50% of maximal decrease), the 40 Hz ASSR requires a higher concentration of sufentanil than does the SEF.

The other parameters did not differ between the ASSR and SEF. The mean values for gamma (which estimates the slope of the concentration effect curve) and for $t_{1/2} K_{eo}$ (which estimates the half-life for drug transfer from the central compartment to the effect site) were similar for ASSR and SEF.

FIGURE 5 Sufentanil plasma concentration as a function of time for each patient.

Results obtained with the derived E_0 method yielded results similar to those obtained with the fixed E_0 method (Table II). For ASSR, derived E_0 was $0.39 \pm 0.21 \mu V$; E_{max} $0.36 \pm 0.20 \mu V$; gamma 4.8 ± 2.0 ($n = 8$; patient H excluded as in Table II); IC_{50} 2.1 ± 0.8 $ng \cdot ml^{-1}$. For SEF, derived E_0 was 24.1 ± 4.2 Hz; E_{max} 21.2 ± 7.1 Hz; gamma 6.7 ± 5.6 ; IC_{50} 1.4 ± 0.7 $ng \cdot ml^{-1}$ ($P < 0.05$ compared with IC_{50} for ASSR). Estimation of K_{eo} is conducted before application of the sigmoid E_{max} model and is thus not influenced by choice of E_0 .

Discussion

The ASSR and SEF followed different time courses during induction of anaesthesia: SEF decreased progressively whereas ASSR increased before falling abruptly (Figure 4). Pharmacodynamic modelling suggests that this difference arises from a difference in sensitivity to sufentanil rather than in the slope of the concentration-effect curve. The concentration of sufentanil required to produce 50% of the maximal attenuation (IC_{50}) was 2.1 ± 1.2 $ng \cdot ml^{-1}$ for the ASSR and 1.4 ± 0.7 $ng \cdot ml^{-1}$ for the SEF ($P < 0.05$). The slope of the concentration-effect curve (gamma) was similar for both measures (6.00 ± 3.69 for the ASSR and 5.87 ± 5.2 for the SEF) (Table II).

The increase in the amplitude of the 40 Hz ASSR during the first four minutes of the infusion of sufentanil is surprising. How can we explain this observation?

TABLE II

Patient	E_0 Hz	E_{max} (Hz)	SEF		
			gamma ($ng \cdot ml^{-1}$)	IC_{50} (min)	$t_{1/2}K_{eo}$
A	25.7	22.4	3.64	1.4	9.1
B	22.2	24.0	0.68	0.8	11.2
C	23.4	18.5	9.96	2.5	8.8
D	22.5	18.7	6.31	2.3	7.0
E	25.7	25.1	0.59	0.9	4.9
F	22.2	15.9	13.91	1.0	4.9
G	28.3	24.5	1.17	0.5	4.0
H	24.5	19.6	12.52	1.4	6.1
J	28.9	23.6	4.05	1.5	5.4
Mean	24.8	21.4	5.87	1.4	6.8
SD	2.5	3.3	5.17	0.7	2.4

Patient	E_0 μV	E_{max} (μV)	40-HZ ASSR		
			gamma	IC_{50} ($ng \cdot ml^{-1}$)	$t_{1/2}K_{eo}$ (min)
A	0.19	0.17	7.13	1.5	12.1
B	0.35	0.32	13.48	0.4	5.5
C	0.33	0.24	4.18	4.2	6.7
D	0.17	0.15	3.11	2.5	6.4
E	0.31	0.31	1.62	1.6	4.5
F	0.59	0.53	3.99	1.4	5.3
G	0.60	0.58	7.56	1.5	7.4
H	0.25	0.22	(31.9)*	2.3	10.2
J	0.39	0.32	6.89	3.4	7.6
Mean	0.35	0.32	6.00	2.1 ¹	7.3
SD	0.16	0.15	3.69	1.2	2.4

*Value excluded as outlier
¹ $P < 0.05$, compared with SEF
 E_0 : baseline value; E_{max} : maximal decrease caused by sufentanil
gamma: parameter of sigmoidicity; IC_{50} : concentration of sufentanil ($ng \cdot ml^{-1}$) that produces 50% of maximal decrease;
 $t_{1/2}K_{eo}$: equilibration half-life for transfer between the central and effect compartments

We think that amplitude of the ASSR increased because the patients became more attentive during induction. They were told they would soon fall asleep and asked to concentrate on their breathing. Anxiety may also have enhanced attention. Attention and arousal augments 40 Hz rhythms in animals¹⁴ and possibly in humans.¹⁵ Muscle rigidity during induction did not contribute substantially to the increase in ASSR amplitude. The contamination of the ASSR traces by muscular artefacts was modest and occurred only during the first minute. A biphasic response to sufentanil is a possible but unlikely explanation for the increased ASSR amplitude.

Did the initial increase in the amplitude of the ASSR contribute to the difference in IC_{50} between ASSR and SEF? If we accept that producing unconsciousness in patients who are attentive and perhaps anxious requires more anaesthetic and that heightened arousal from attention or anxiety increases the amplitude of ASSR without changing SEF, then the answer is yes. We do

not think however that the increase of ASSR amplitude did interfere with pharmacodynamic modelling. Similar results were obtained by letting the programme derive the baseline E_0 . This procedure estimates the initial values (E_0) assuming that no increase occurred.

The $t_{1/2} k_{eo}$ obtained for SEF is similar to that reported by Scott *et al.*⁸ but our estimates of the IC_{50} for the SEF is about twice that reported by Scott *et al.* A literature search did not reveal other estimates for the IC_{50} of sufentanil for EEG measures. We do not have a firm explanation for our highest IC_{50} . Midazolam, which was used as an anxiolytic in this study but not by Scott *et al.*, may be a factor. The effect of midazolam on the EEG is to enhance fast (beta) activity,¹⁶ in contrast to opioids which enhance slow activity. Increased beta activity would have resulted in a high baseline SEF, which was not observed. Nevertheless, it is conceivable that midazolam would have counteracted the EEG effects of sufentanil. The effects of midazolam on the ASSR have not been described.

Studying concentration-effect relationships in the clinical context of coronary artery surgery imposed several limitations. The duration of the study was limited to 30 min from the beginning of the sufentanil infusion. The documentation of the offset of action was incomplete. The dose was higher than in studies performed with volunteers.⁵ Finally it was necessary to provide an anxiolytic medication (midazolam) because anxiety can precipitate angina.¹⁷ We conclude that the sufentanil IC_{50} for ASSR is higher than for SEF, at least in the presence of sedation with midazolam. The results reveal a functional difference between ASSR and SEF as CNS measures of opioid effect.

Acknowledgments

We thank Peter, April and Richard Mowrey for programming, The Minh Tu for the sufentanil assay, and Julie Pelletier for preparing most figures.

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