ELECTROENCEPHALOGRAPHIC EFFECTS OF SUFENTANIL ANAESTHESIA IN MAN

J. G. BOVILL, P. S. SEBEL, A. WAUQUIER AND P. ROG

SUMMARY

The effects of anaesthesia with sufentanil 15 μg kg⁻¹, air and oxygen on the electroencephalograph were studied in 12 patients before and after cardiopulmonary bypass. The e.e.g. responses were characterized by high voltage, slow delta waves. Although the mean power in the delta band declined with time, the contribution of delta power to total power in the frequency range 0.5-40 Hz remained constant until the onset of cardiopulmonary bypass. Sharp waves of uncertain neurophysiological significance were seen. They were not associated with clinical signs of epileptic activity. The use of the e.e.g. response as a monitor of “depth of anaesthesia” during high-dose opioid anaesthesia may become possible.

The use of large doses of opioid analgesics as anaesthetic agents for cardiac surgery was proposed by Lowenstein and colleagues (1969) who used morphine 0.5–3.0 mg kg⁻¹ as the anaesthetic. More recently, anaesthesia with fentanyl 50–100 μg kg⁻¹ has been advocated (Stanley and Webster, 1978; Lunn et al., 1979) since, in addition to providing a high degree of cardiovascular stability, fentanyl anaesthesia decreases the hormonal responses to surgery, although those to cardiopulmonary bypass are unaffected (Stanley et al., 1980; Sebel et al., 1981a).

Sufentanil is a synthetic opioid analgesic. It is extremely potent, being 4520 times as potent as morphine in the tail withdrawal test in rats and is also safe, the LD₅₀/ED₅₀ ratio in rats being 25211 (morphine = 67, fentanyl = 277). Dogs given sufentanil 5 μg kg⁻¹ have survived and recovered after 96 h (Niemegeers et al., 1976).

Clinical experience in man suggests that sufentanil is five to 10 times as potent as fentanyl and produces minimal cardiovascular depression (de Castro, 1976; Van de Walle, Lauwers and Andrielsen, 1976; Rolly, Kay and Cockx, 1979). Reddy and colleagues (1980) demonstrated that infusions of sufentanil up to 40 μg kg⁻¹ min⁻¹ produced little change in cardiovascular dynamics in dogs treated with atropine and have suggested that the drug be evaluated as an anaesthetic in man.

As a part of this evaluation, we have studied the effects of anaesthesia with sufentanil 15 μg kg⁻¹ on the electroencephalogram in patients undergoing cardiac surgery.

PATIENTS AND METHODS

Twelve patients undergoing coronary artery bypass (nine patients) or valve replacement (three patients) surgery were studied. The mean age was 57 ± 2.1 yr and the mean weight 74 ± 2.7 kg. Informed consent was obtained at the pre-operative visit.

The patients were premedicated with lorazepam 4–5 mg by mouth 1.5 h before surgery. A radial artery cannula, a central venous catheter and two wide-bore peripheral cannulae were inserted percutaneously under local analgesia before the induction of anaesthesia and e.e.g. electrodes were applied. Silver chloride “stick-on” electrodes were fixed to the scalp with 8% collodium to permit e.e.g. recording. Records were obtained on an eight-channel Beckman Accutrace recorder with the amplifiers set at 50 μV cm⁻¹, filters at 50 Hz and time constant at 0.3 s. The leads used were:

1. Left fronto-polar→left mid-temporal (F₉₉–T₃₉)
2. Left mid-temporal→left occipital (T₃₉–O₁₀)
3. Right fronto-polar→right mid-temporal (F₉₂–T₄₉)
4. Right mid-temporal→right occipital (T₄₂–O₁₂)
5. Left mid-temporal→vertex (T₃₉–C₀₁₀)
6. Vertex→right mid-temporal (C₀₁₀–T₄₁₀)

© Macmillan Publishers Ltd 1982
The e.c.g. was recorded on channel 7 and eye movement derived from an electrode placed on the infra-orbital margins was recorded on channel 8. Derivation 5, T3-C0, was recorded onto magnetic tape using a Tandberg Instrumentation Tape Recorder (series 100) for subsequent off-line computer analysis.

Following a control period of at least 6 min, pancuronium 2 mg was administered i.v. and anaesthesia induced with sufentanil 15 mg kg⁻¹ i.v. over 2 min. Pancuronium 6 mg was administered when the patient became unresponsive. The lungs were ventilated manually for 5 min, the trachea intubated and artificial ventilation was continued with an air and oxygen mixture (FIO₂, 0.5). A nasogastric tube was inserted and thermocouples positioned. The e.e.g. was recorded continuously until the start of cardiopulmonary bypass. E.e.g. analysis was not attempted during cardiopulmonary bypass because of the changes associated with hypothermia (26 °C) and bypass. Following bypass the e.e.g. was recorded intermittently on paper. A visual interpretation of all the paper records was made by one of the authors (P. R.). Subsequent off-line computer analysis was carried out using a PDP11/E10 computer system. Power spectral analysis, using a Fast Fourier Transformation, was carried out for each 30-s epoch and the power contained in the frequency bands, delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-13.0 Hz) and beta (13.0-25.0 Hz) calculated.

Digitization at a rate of 200 s⁻¹ allowed a frequency band pass band of 0-100 Hz, resolution ±0.2 Hz. Spindle power was also calculated. The power in the various bands was then plotted on an

![Graph](image)

FIG. 1. Example of the e.e.g. after premedication. Leads 1-8 are as described in methods. This shows fast-wave activity with some muscle activity. The "waves" at 4.5 and 7 s are a result of eye movements.
FIG 2. Example of the e.e.g. 1 min after start of induction. Leads 1–8 are as described in methods. The overall activity is slower. Theta activity is seen and a slow eye movement is seen in lead 8.

**X–Y recorder.** Three-dimensional power spectral analysis was performed for the frequency range 0.5–15 Hz.

Data analysis of the e.e.g. signals for the group of 12 patients was carried out using the technique described by Wauquier and others (1979). Essentially, the mean power in each of seven pre-defined frequency bands from 0.5 to 40 Hz was calculated for each 6 min 15 s recording time (4 min 36 s analysis time + calculation and printing time). This was repeated for each record. Relative power was calculated as follows: for each time interval the total power (0.5–40.0 Hz) was equalized at 100% and the relative contribution to the total power contained in each of the pre-defined frequency bands calculated. All patients were visited by one of the authors (P. R.) 4–5 days after surgery and questioned as to awareness or memories of the procedure.

**RESULTS**

The appearance of the e.e.g. following the administration of sufentanil was similar in all patients. Typical examples of the changes observed are shown in figures 1–3. Within 30–60 s from the start of induction, the alpha rhythm became slower and broader and slow eye movements were seen. This was followed rapidly by diffuse theta activity and some delta waves. Delta activity increased, and by 3 min after the start of induction, there was continuous high voltage slow (0.5–2 Hz) delta wave activity which became synchronized in 50% of the patients. During the following 10–15 min, the e.e.g.
became more irregular with a lower voltage, and theta activity again became obvious after which the pattern remained constant until the onset of cardiopulmonary bypass. No changes in the e.e.g. were observed in any patient during tracheal intubation, skin incision or sternotomy. Following skin incision, diathermy caused considerable interference to the e.e.g. signal, although there were always sufficient uninterrupted segments available for visual analysis. After cardiopulmonary bypass, delta activity remained evident although the amplitude was less and there was an increase in theta activity. Intermittent alpha activity was observed at the end of the operation in only one patient, 5 h after induction.

Isolated sharp wave activity was observed in all patients within 2 min of induction (fig. 3). This was most obvious in the fronto-temporal region and occurred with a frequency of 8–12 min⁻¹ during the initial 10–15 min and then disappeared in all but two patients, in whom they continued until the onset of cardiopulmonary bypass. They were mainly tri-phasic with a period of 30–60 ms and an amplitude of 10–70 μV. Sharp wave activity was never seen after bypass and was not associated with other signs of epileptic activity.

A representative example of three-dimensional power spectral analysis from one patient is shown in figure 4 and wide-band power spectral analysis from the same patient in figure 5. In the period before the induction of anaesthesia there was predominant beta-activity and to a lesser extent alpha-activity in all patients. Immediately following the injection of sufentanil, the power in the alpha and beta bands decreased, whereas it increased in the theta and delta bands. However within 10–15 min of induction the theta power
E.E.G. EFFECTS OF SUFENTANIL

had decreased to pre-induction values. Delta band power also decreased slightly during this period and then remained constant until the start of bypass. Neither tracheal intubation nor surgical stimuli altered the spectral pattern. During the time of the skin incision the computer was unable to analyse segments containing artefacts caused by diathermy.

The power spectral analysis for the group of 12 patients for the frequency range 0.5-40.0 Hz is shown in figure 6 and the relative power in figure 7. Total power increased following induction with sufentanil, being maximum between 12 and 18 min. This increase was predominantly because of an increase in the power in the delta (0.5-3.5 Hz) and theta (3.5-7.5 Hz) bands. The power in the theta band then decreased to pre-
FIG 6. Absolute e.e.g. power (mW) for 12 patients, plotted as mean ± SEM in the following bands: delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-9.5 Hz), alpha\textsubscript{2} (9.5-15 Hz), beta (13.5-17.5 Hz), beta\textsubscript{2} (17.5-25 Hz), beta\textsubscript{3} (25-40 Hz) and total power in all bands. The peak in the beta\textsubscript{2} band at 80 min was caused by an artefact. The decrease in absolute delta power with time is seen.

FIG 7. Relative e.e.g. power (%) as a percentage of total power (equalized at 100%) in the following bands: delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-9.5 Hz), alpha\textsubscript{2} (9.5-15 Hz), beta (13.5-17.5 Hz), beta\textsubscript{2} (17.5-25 Hz), beta\textsubscript{3} (25-40 Hz) and total power in all bands. The peak in the beta\textsubscript{2} band at 80 min is a result of artefact. This plot shows that, although the absolute power in the delta band decreased with time, the relative contribution to total power remained very constant.


E.E.G. EFFECTS OF SUFENTANIL

Induction values. Delta power also decreased but always remained considerably greater than its pre-induction value. The relative contribution of the power in the delta band to total power remained constant until the onset of cardiopulmonary bypass (fig. 7). The relative contribution to total power from the other bands decreased and then remained constant at a very low level. After direct questioning, no patient reported any awareness during the operation. The first memory after surgery, in all patients, was of being in the intensive care unit.

DISCUSSION

The electroencephalographic effects of small doses of fentanyl and sufentanil (fentanyl 0.4–0.6 mg, sufentanil 0.04–0.06 mg, total doses) have been studied in man in combination with droperidol 15–20 mg and nitrous oxide by Kubicki and colleagues (1977). The only significant change they found was an increase in delta power by a factor of 10. The electroencephalographic effects of higher doses of fentanyl (30–70 µg kg^-1 with and without nitrous oxide) were investigated by us in a previous study (Sebel et al., 1981b) in which it was observed that fentanyl 50–70 µg kg^-1 produced a characteristic e.e.g. response; a massive increase in delta power. Fentanyl 30 µg kg^-1 produced a different e.e.g. pattern with less delta activity and was clinically inadequate as an anaesthetic. Nitrous oxide did not affect the electroencephalographic responses to fentanyl and from the electroencephalographic standpoint does not appear to be a necessary component of an opioid anaesthetic technique. For this reason, and the fact that nitrous oxide may cause cardiovascular depression in combination with an opioid analgesic (McDermott and Stanley, 1974; Lunn et al., 1979) nitrous oxide was not used in this study.

The e.e.g. responses to sufentanil 15 µg kg^-1 are indistinguishable from those seen after fentanyl 50–70 µg kg^-1. This is in keeping with the similarity in the pharmacological profiles of the two compounds. The decrease in total power in the e.e.g. with respect to time was also seen with fentanyl. The constancy of the delta band contribution to total power suggests that this may be useful as an index of anaesthetic depth during opioid anaesthesia, and is worthy of further study in a situation where the e.e.g. is not affected by cardiopulmonary bypass. Another way of using the e.e.g. as a guide to the depth of anaesthesia would be to look at the recovery of the higher frequency activity. It is not yet clear how the e.e.g. varies during the recovery period, but initial results suggested that power in the higher (beta) frequency bands may increase linearly with respect to time. Unexpectedly, a similar response was not seen in the delta band. Although delta power decreased during the first 3–4 h after operation, sporadic increases then occurred during the next few hours. These may result from the recurrence of episodes of a natural non-REM sleep pattern, which is also characterized by high powered delta activity (Sebel, P. S. and Bovill, J. G., unpublished observations).

During arousal from sleep, the e.e.g. changes from high voltage slow waves to low voltage fast waves and such an e.e.g. response has been demonstrated following skin incision during halothane anaesthesia in adult man (Oshima, Shirgu and Mori, 1981). This suggests that reappearance of fast wave activity in response to a specific stimulus may be an indication that anaesthesia is becoming "light". There were no e.e.g. responses to the stimuli of intubation or surgery in any patient in this study or during the investigation under fentanyl anaesthesia (Sebel et al., 1981b). This may indicate that opioid analgesics are more effective than inhalation agents in blocking cortical arousal during surgery.

The sharp waves seen after sufentanil are similar to those we have described after the administration of fentanyl (Sebel et al., 1981b). They do not resemble epileptic spike waves and never became generalized, nor were they associated with any clinical signs of epileptic activity. Their neurophysiological significance remains uncertain. Similar sharp waves have been described in dogs following the administration of opioid analgesics (Wauquier et al., 1981), and after the injection of β-endorphin into the cerebral ventricles of rats (Havlíček et al., 1980). We conclude that sufentanil anaesthesia produced an e.e.g. response characterized by high voltage slow delta waves. This response is similar to that produced by high-dose fentanyl anaesthesia.

REFERENCES

BRITISH JOURNAL OF ANAESTHESIA

EFFETS ELECTROENCEPHALOGRAPHIQUES DE L'ANESTHESIE AU SUFENTANIL CHEZ L'HOMME

RESUME

Les effets de l'anesthésie provoquée par 15 μg kg⁻¹ de sufentanil, l'air et l'oxygène sur l'electroencephalogramme ont été étudiés sur 12 patients, avant et après une dérivation cardiopulmonaire. Les réactions à l.e.e.g. ont été caractérisées par des ondes delta lentes à haute tension. Bien que la puissance moyenne de la bande delta ait diminué avec le temps, la contribution de la puissance totale dans la plage des fréquences 0,5–40 Hz est restée constante jusqu’au début de la dérivation cardiopulmonaire. On a vu des ondes accentuées d’une signification neurophysiologique incertaine. Elles n’ont pas été associées aux signes cliniques d’une activité épileptique. On pourrait envisager d’utiliser les réactions à l.e.e.g. pour la surveillance de la profondeur de l’anesthésie pendant toute la durée d’une anesthésie basée sur de fortes doses de substances opiacées.

ELEKTROENZEPHALOGRAPHISCHE AUSWIRKUNGEN EINER SUFENTANIL-ANÄSTHESIE BEIM MENSCHEN

ZUSAMMENFASSUNG


EFECTOS ELECTROENCEFALOGRAFICOS DE LA ANESTESIA MEDIANTE SUFETANIL EN EL HOMBRE

SUMARIO

Se estudiaron en 12 pacientes los efectos de la anestesia efectuada con 15 μg kg⁻¹ de sufentanilo, aire y oxígeno, en el electroencefalograma, antes y después de llevar a cabo una desviación cardiopulmonar. Las respuestas del e.e.g. se caracterizaron por ondas delta, lentas y de alto voltaje. Aunque la potencia media en la banda delta declinó con el paso del tiempo, la contribución de la potencia delta a la potencia total, en la gama de 0,5 a 40 Hz, permaneció constante hasta el comienzo de la desviación cardiopulmonar. Se contemplaron ondas muy agudas cuyo significado neurofisiológico es incierto. Estas no vinieron asociadas con signos clínicos de actividad epiléptica. Puede que llegue a ser posible usar la respuesta del e.e.g. cuál un monitor de la “profundidad de la anestesia” durante aquella efectuada con grandes dosis de opioides.