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Effects of High-dose Fentanyl Anesthesia on the Electroencephalogram

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The purpose of this study was to define the EEG changes produced in humans by fentanyl 30–70 μg/kg during cardiac surgery. The authors have also assessed awareness in the patients. Thirty-nine patients were studied; oral lorazepam or intramuscular morphine was used as premedication. Anesthesia was induced with intravenous injection of fentanyl over 2 min and the patients were ventilated with either air/O_2 (24 patients) or N_2O/O_2 (15 patients). The EEGs recorded until the start of cardiopulmonary bypass were visually analyzed, classified into EEG stage, and plotted graphically as narcograms. Computerized 3-dimensional power spectral analysis and wide band spectral analysis were carried out on representative EEGs. The EEG effects of fentanyl are consistent and are characterized by high-voltage slow delta waves. Nitrous oxide had no effect on the EEG responses to fentanyl. Computer analysis confirmed the visual interpretation. There was no incidence of awareness. The authors conclude from this study that fentanyl after premedication is a suitable drug for providing unconsciousness, analgesia, and amnesia during cardiac surgery. (Key words: Analgesics: fentanyl. Anesthesia: cardiovascular. Anesthetics, intravenous: fentanyl. Brain: electroencephalography.)

BECAUSE of its ability to produce a high degree of cardiovascular stability, morphine (0.5–3.0 mg/kg) has been used extensively for anesthesia during cardiac surgery.[1] However, this technique is not without disadvantages. Hypertension may occur, probably related to an increase in circulating catecholamines.[2] Hypotension can also occur, possibly caused by histamine release.[3] The main disadvantage of morphine is its inability to produce complete anesthesia, the occasional patient being aware during surgery. This occurs most frequently in patients who have not had prolonged serious illness, *e.g.*, patients undergoing coronary artery surgery. In many such patients it may not be possible to induce anesthesia with morphine alone.[3]

Intravenous fentanyl (up to 75 μg/kg) has been proposed as an improvement on morphine anesthesia, producing minimal cardiovascular changes in patients undergoing mitral valve surgery[4] and coronary artery surgery.[5]

There is no information as to whether fentanyl is capable of producing a state of anesthesia. The purpose of this study was to investigate the effects of high-dose fentanyl anesthesia on the electroencephalogram in humans premedicated with lorazepam or morphine, and to determine the incidence of awareness, if any, during cardiac surgery using this technique.

Methods

Six groups of patients undergoing elective or emergency cardiac surgery were studied (table 1). The dose of fentanyl used was from 30–70 μg/kg. Lorazepam (4 mg < 65 kg bodyweight, 5 mg > 65 kg bodyweight) was given orally as premedication 1.5 h before surgery except in one group of nine patients who were given morphine, 10 mg, im.

Before induction, a radial artery cannula, a central venous catheter and two wide-bore peripheral catheters were inserted percutaneously under local anesthesia. Silver chloride "stick on" electrodes were applied to the scalp for EEG recordings, which were made on an 8-channel Beckman® Accutrace recorder with the amplifiers set at 50 μv/cm, filters at 50 Hz, and time constant at 0.3 s. The leads used were: 1) left fronto-polar → left midtemporal ($F_{p1} \rightarrow T_3$), 2) left midtemporal → left occipital ($T_3 \rightarrow O_1$), 3) right fronto-polar → right midtemporal ($F_{p2} \rightarrow T_4$), 4) right midtemporal → right occipital ($T_4 \rightarrow O_2$), 5) left midtemporal → vertex ($T_3 \rightarrow C_0$), 6) vertex → right midtemporal ($C_0 \rightarrow T_4$), 7) ECG, and 8) eye movements.

Following a control period, anesthesia was induced with the appropriate dose of fentanyl, given intravenously over 2 min, followed by 8 mg pancuronium for neuromuscular blockade. The patient was ventilated manually for 5 min and then intubated. Ventilation was continued with either air/O_2 or N_2O/O_2 ($F_{IO_2} = 0.5$). A nasogastric tube was passed and thermocouples positioned. The EEG, ECG, blood pressure, and central venous pressure were continually monitored until the start of cardiopulmonary bypass. Because of the EEG changes associated with cooling and bypass, EEG analysis was not attempted during cardiopulmonary bypass. The EEG was intermittently recorded after bypass.

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TABLE 1. Patient Groups

	Premedication					
	Lorazepam	Lorazepam	Lorazepam	Lorazepam	Morphine	Lorazepam
Fentanyl dose (μg/kg)	30	50	60	60	60	70
Gases used	N_2O/O_2	N_2O/O_2	N_2O/O_2	Air/O_2	Air/O_2	Air/O_2
Number of patients	5	5	5	5	9	10
Male	5	4	5	5	8	8
Female	—	1	—	—	1	2
Mean age (yr) (±SD)	57.4 ± 5.31	61.4 ± 8.86	62.8 ± 5.23	59.8 ± 10.16	60.1 ± 13.34	52.9 ± 12.05
Mean weight (kg) (±SD)	69.8 ± 7.96	75.2 ± 6.52	76.6 ± 9.58	67.8 ± 2.48	68.9 ± 6.20	68.2 ± 9.55
Coronary artery surgery	5	4	5	4	6	7
Valve replacement	—	1	—	1	3	3

The EEG recordings were later analyzed visually and classified into "EEG levels" using a classification described by Kugler[6] (table 2). For each 20-s epoch from before induction until 30 min after induction, then for each 60-s epoch until bypass, an EEG level was determined. These levels were then plotted as "narcograms", graphical representations of EEG levels. All visual analysis of the EEGs was performed by one of the authors (P.R.). Fifteen EEGs were analyzed at least 3 months after the first analysis and no variation greater than 1 EEG level was found. Two EEGs were analyzed by an independent observer and no variation found. For each group, the mean EEG level at each time point was calculated and a mean narcogram plotted.

In order to define the difference between groups, regression analysis was carried out for each group using the EEG levels from 15–70 min, when the levels were stable (an interval of 15–55 min was used in the 30 μg/kg group). The 95 per cent confidence interval for the midpoint (42 min) of the regression line was calculated.[7]

The EEG from at least one patient in each group was recorded on magnetic tape and subsequently computer analysis carried out using a PDP11/E10 computer. Power spectral analysis, using a Fast Fourier Transformation was carried out on one cortical derivation for each 30-s epoch, and the power contained in the delta (0.5–3.5 Hz), theta (3.7–7.5 Hz), alpha (7.5–13.0 Hz) and beta (13.0–

TABLE 2. EEG Classification

Clinical State	EEG Level	Specific EEG Appearance	Reactions to Stimuli Special Features	General EEG Picture
Awake	A_0	Normal variations	Visual Block Reaction (VBR)	Alpha rhythm
Reduced vigilance	A_1	Alpha rhythm broader and somewhat slower	Reduced VBR	Synchronized
	A_2	Paroxysmal disappearance of alpha rhythm; some theta waves, maximal frontally	Changing VBR	
	B_0	Slow alpha waves mixed with theta	Negative VBR	Desynchronized
	B_1	Increased beta and theta activity (maximal temporal-parietal)	Slow eye movements	
	B_2	As B_1 but higher voltage with some vertex waves	Low voltage vertex waves	
Light sleep	C_0	Increased theta activity up to 30 per cent of the time	K complexes with spindle activity (12–15 ps)	Vertex activity
	C_1	Theta 30–50 per cent		
	C_2	Continuous slow theta activity		
Moderately deep sleep	D_0	Increase in delta activity to 30 per cent of the time	Broad K complexes with spindle activity (10–12 ps)	Polymorphic
	D_1	Delta 30–50 per cent		
	D_2	Delta 50–80 per cent (slower)		
Deep sleep	E_0	Continuous delta activity		Monomorphic
	E_1	Continuous delta >300 μV		
	E_2	As E_1 but slower than 0.25/s		
Coma	F	As E but with flat curves		Slow with flat periods

* Visual Block Reaction is the disappearance of alpha rhythm that occurs on eye opening in the awake patient.

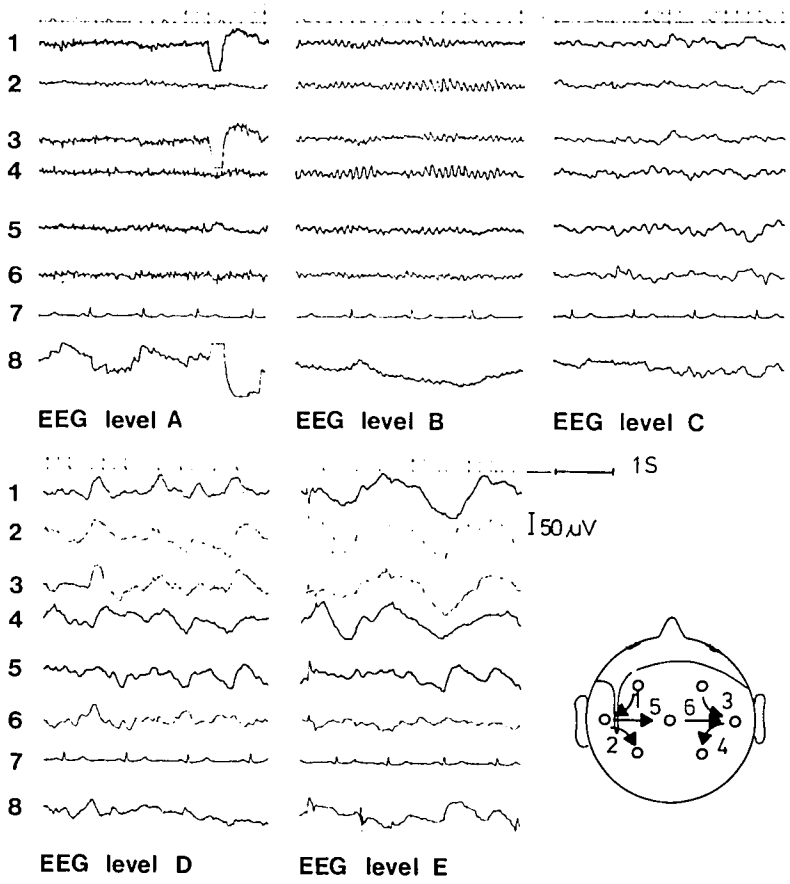

FIG. 1. Example of EEG following lorazepam premedication, fentanyl, 60 μg/kg, N_2O/O_2. Leads 1–8 are described in the Methods section. EEG level A shows normal awake pattern with eyes open. Eye movements can be seen in channels 1, 3, and 8. EEG level B shows diffuse slow alpha activity. Level C shows theta waves with some delta waves. Level D shows increasing delta activity. Some theta activity is still present. Level E shows synchronized high voltage slow delta waves.

25 Hz) frequency bands calculated. Spindle power was also calculated. The power in the varying bands was then plotted on an X-Y recorder.

Three-dimensional power spectral analysis of the square root of the power was also performed for the frequency range 0.5–15 Hz for each 50-s epoch. Statistical analysis of the power spectrum was carried out for one group (five patients lorazepam, fentanyl 70 μg/kg, air/O_2). The mean power (±SD) was computed for each of seven predefined frequency bands over each 6-min, 15-s epoch of EEG recording and plotted graphically.

Systolic and diastolic blood pressure and heart rate were recorded before induction, after induction, after incision and after sternotomy.

Statistical analysis of cardiovascular data was carried out using analysis of variance. A modified t test was used to identify significant differences from preinduction values using critical values for P calculated according to the method of Bonferroni.

Every patient was visited by one of the authors (P.R.) 4–5 days after surgery and closely questioned about memories of the anesthetic and surgical procedure.

Results

EEG Appearance

Fentanyl produced consistent EEG changes. Typical examples of EEG changes are shown in figure 1. Within 40–60 s of the start of induction, the alpha rhythm (9–13 Hz) became slower and broader and slow eye movements were seen (level B). By 60–150 s, diffuse theta waves (4–8 Hz) were seen (level C) and some delta activity (<3 Hz) occurred, maximal frontally (level C–D). This was rapidly followed by irregular diffuse slow delta waves (level D). After about 150 s the delta waves became more synchronous, with a monomorphic EEG picture (level E). Not all patients reached level E. After about 4 min, the EEG appearance was more irregular, somewhat faster and of slower voltage (level D). The pattern then changed very little until the start of cardiopulmonary bypass. The EEG appearance was very similar in all groups except the 30 μg/kg group which showed significantly faster activity. Most patients showed some spindle activity but K complexes were never seen.

In some patients isolated sharp wave activity was

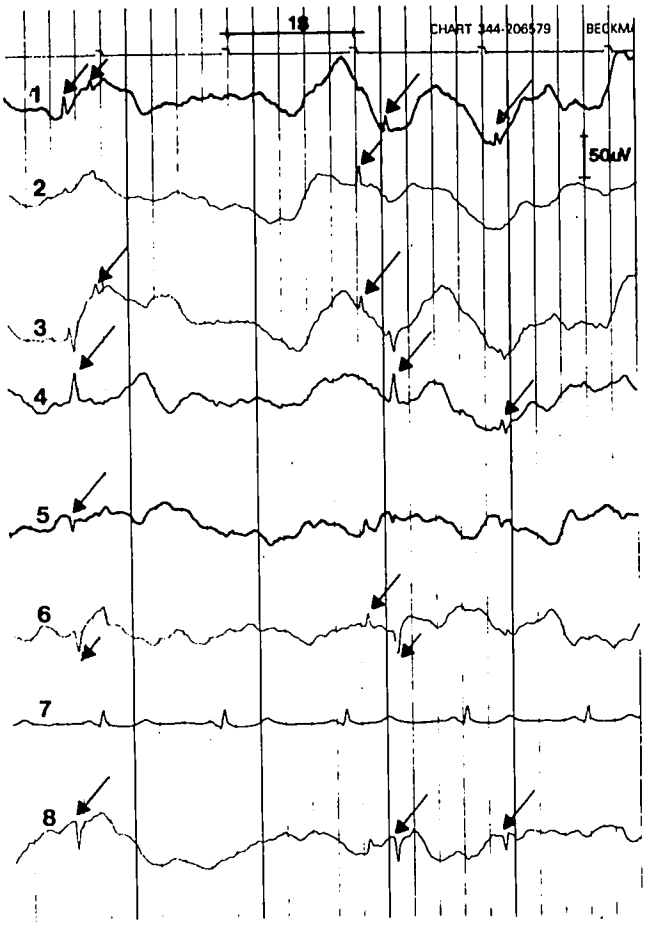

FIG. 2. Example of sharp waves in the same patient. Leads 1–8 are as described in the Methods section. The EEG level is E. The low-voltage sharp waves are indicated by arrows.

seen about 2 min after the start of induction (fig. 2). It was more evident with increasing doses of fentanyl, being present in 20 per cent of patients at 30 μg/kg, 60 per cent at 50 μg/kg, 58 per cent at 60 μg/kg and 80 per cent at 70 μg/kg. This activity was mainly localized to the frontotemporal region and did not generalize. It was of different duration in each patient, varying from 3 min until the start of bypass. Sharp wave activity was never seen after cardiopulmonary bypass and was not associated with any other signs of epileptic activity.

There were no EEG changes seen in any patient in response to the stimuli of intubation or surgery. Although diathermy interference after skin incision was present, there were always sufficient uninterrupted segments of EEG available for visual analysis. In the period between discontinuation of cardiopulmonary bypass and the end of surgery the EEG level remained between C_1 and D_1.

NARCOGRAMS

An example of a single nacrogram is shown in figure 3. Figure 4 shows the mean narcograms of the first two groups studied, lorazepam premedication, fentanyl 60 μg/kg with and without nitrous oxide. There was very little difference between these 2 groups and figure 5 shows the mean of these two groups plotted against the other study groups. From 2 min after the end of induction until the start of bypass, the maximum range of EEG level at any time point in any group was three levels except in the 30 μg/kg group which showed greater variation.

The narcograms show that, following induction, there was a rapid fall in the EEG level, maximum at 2–3 min after induction in every group. This was followed by an increase over the next 10–13 min of between one and two EEG levels and then the level was stable until the start of bypass. Figure 5 shows that for the 30 μg/kg group the narcogram was one EEG level lighter than the other groups up to about 55 min when fentanyl supplement was given to one patient because of inadequate anesthesia. At the time of

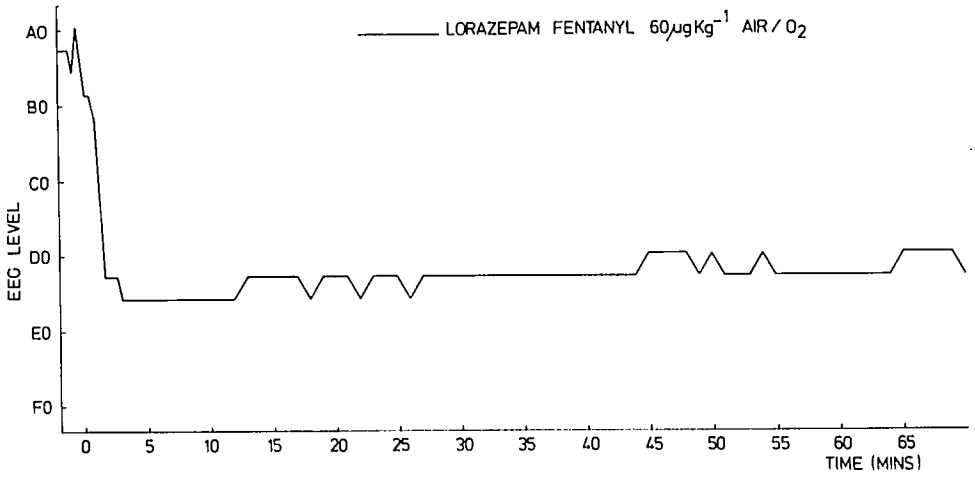

FIG. 3. Example of a single narcogram. The EEG levels are as described in table 2. Fentanyl was given at time 0 min. The rapid fall in EEG level to D_2 is clearly seen. The consistent nature of the EEG is also seen.

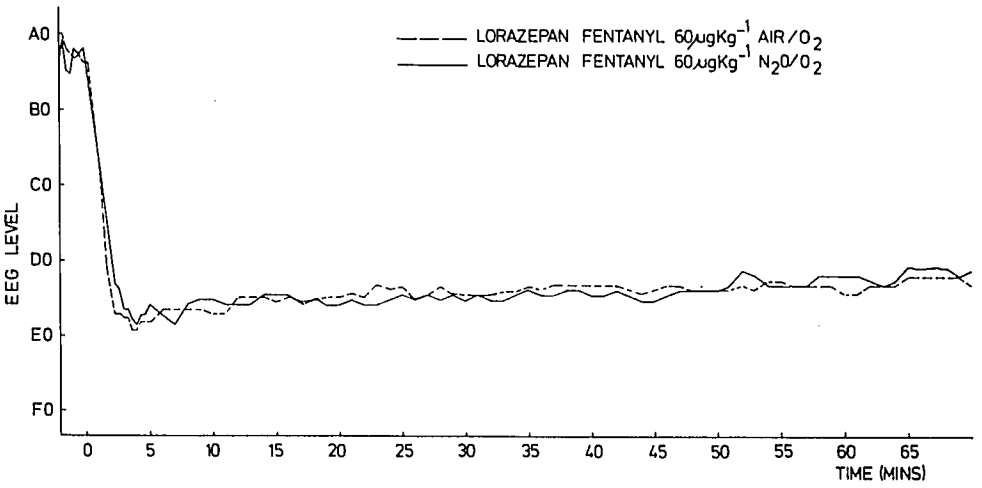

FIG. 4. Mean narcograms for the first two groups studied.

administration of the supplement, the patient was lacrimating and sweating. The systolic blood pressure had increased by 20 torr above control value and the heart rate by 20 beats/min. On subsequent visual analysis of the nacrogram, the EEG level had gradually risen from D_0 to B_1, over the 10 min preceding supplementation of anesthesia.

Figure 6 shows an example of the regression line calculated for a single group of patients. The EEG levels (±95 per cent confidence intervals) calculated from the midpoints (42 min) of the regression lines for all groups are shown in figure 7. Although there is a statistically significant difference between 50, 60 and 70 μg/kg doses, this is probably not clinically significant, considering the inherent inaccuracy (up to one level) in the visual analysis. The 30 μg/kg group was at a significantly lighter level than the other groups.

Computer Analysis

Figure 8 is an example of 3-dimensional power spectral analysis. It shows clearly that on induction with fentanyl, the alpha activity disappeared to be rapidly replaced by high-voltage delta waves, which continue as the major feature until the start of cardiopulmonary bypass. During the incision period, the computer rejected analysis on those segments in which diathermy was present. The peaks seen at the back of the plot are due to pump artifact.

Figure 9 shows the wide band spectral analysis of the same EEG. The power in the delta band (0.5–3.5 Hz) shows a picture similar to an inverted narcogram and provided a computer check on the visual analysis.

Figure 10 shows the statistical analysis of the EEGs from a group of five patients. It gives an indication of range of the powers in the various wavebands. The most striking feature is the large increase in delta power.

Patient Recall

With lorazepam premedication and fentanyl 50–70 μg/kg, there was, in most cases, amnesia for all events after arrival in the operating theater. In a few

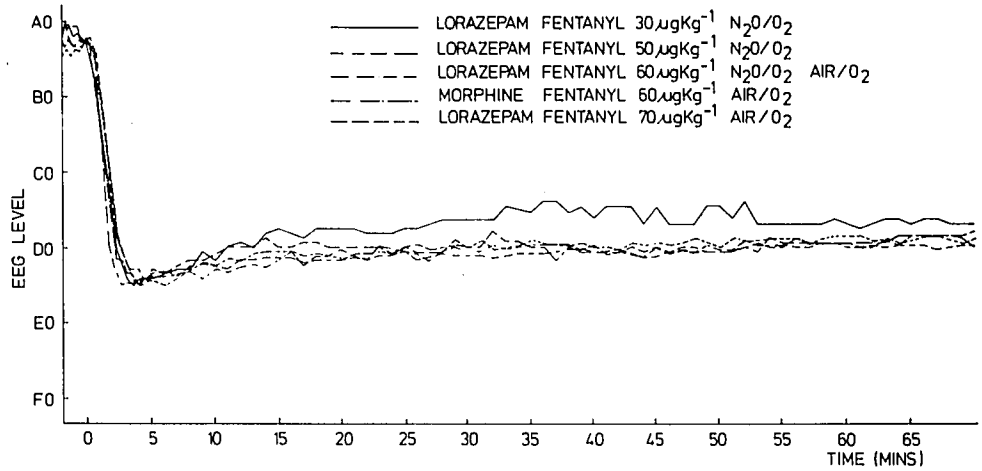

FIG. 5. Mean narcograms for all groups studied. The 30 μg/kg group has a lower EEG level than the other groups until 55 min when fentanyl supplement was given to one patient.

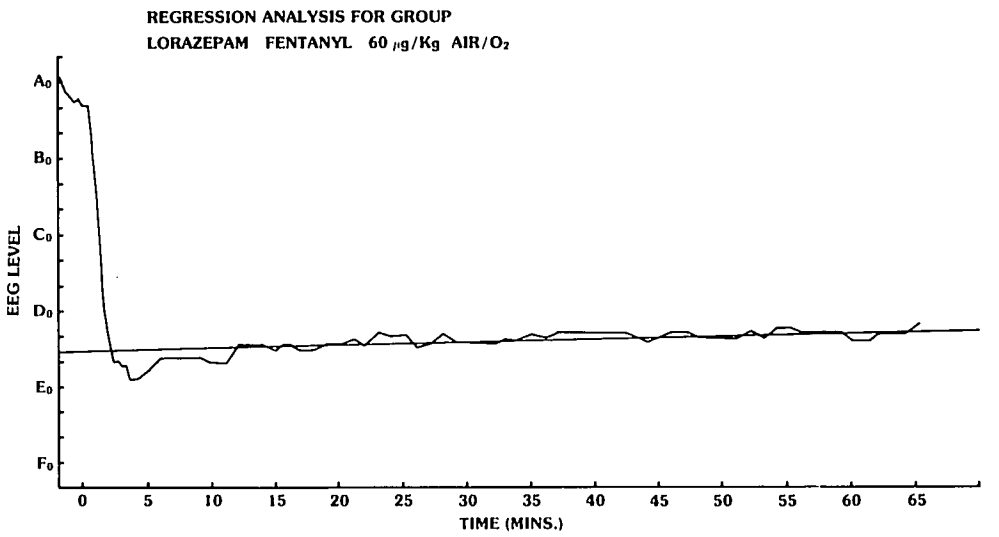

FIG. 6. Regression line drawn for one group. Calculations as described in the Methods section.

patients even this was not remembered. The extent of the amnesia for preinduction events was less in the patients given morphine premedication, but no patient in any group had any memory for events occurring after pre-oxygenation. No patient reported any awareness during surgery.

CARDIOVASCULAR RESPONSES

Cardiovascular data are summarized in table 3. The only significant change at induction of anesthesia was a reduction in systolic pressure in patients who received fentanyl 30 μg/kg. This group also showed a significant increase in systolic pressure and heart rate following sternotomy. The only other significant change in hemodynamics was an increase in diastolic pressure following sternotomy in the patients who received fentanyl 70 μg/kg.

Discussion

Electroencephalography has generally not been considered clinically useful by anesthetists for assessing responses to anesthetic agents. This is partly due to difficulty in interpretation of the EEG pattern and partly because EEG appearance has limited correlation with the clinical status of the patient. However, most anesthetic agents show a specific EEG pat-

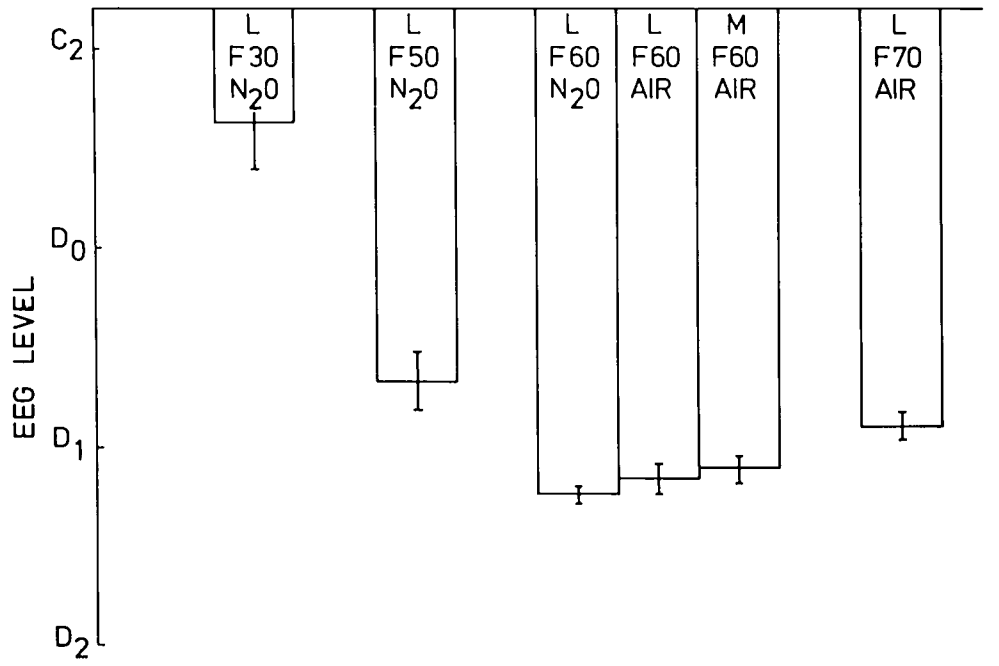

FIG. 7. Mean EEG levels at 42 min. The length of the columns respresent the mean EEG level calculated from regression analysis. The bars represent the 95 per cent confidence intervals for the mean values. L = lorazepam, M = morphine, F30 = fentanyl (30 μg/kg), F50 = fentanyl (50 μg/kg), etc.

tern and these have been reviewed by Stockard and Bickford.[18] The EEG responses to anesthesia have been described by Winters *et al.*[9] as a progression of changes to different levels of excitability or depression associated with a loss of responsiveness and amnesia.

De Castro *et al.*[10] found that fentanyl produced severe convulsions in dogs at 4 mg/kg, iv, and suggested that fentanyl belongs in the group of dominantly excitatory anesthetics. We suggest, in doses up to 70 μg/kg in humans, that the EEG appearance after fentanyl is predominantly one of depression. The only possible excitatory feature seen was the sharp waves. These did not look the same as epileptic spike waves and were never generalized. The significance of these sharp waves remains uncertain but since they appear to be dose-related, further investigation of this phenomenon using fentanyl doses greater than 70 μg/kg is warranted. It is possible to demonstrate either activation of epileptic foci or spike wave activity with all commonly used anesthetics with the exception of halothane.[11]

Klein and Klein[12] studied the effects of fentanyl anesthesia in doses up to 100 μg/kg in dogs and showed that no dose of fentanyl produced a different EEG compared with 70 per cent nitrous oxide alone. EEG responses in humans are not necessarily the same as those seen in animals. In humans, the EEG response to 50 per cent nitrous oxide is loss of alpha rhythm and appearance of theta waves. This is different from the responses to fentanyl anesthesia seen in our series. There was no difference in EEG following fentanyl when ventilation was carried out with either air/O_2 or N_2O/O_2. It is surprising that nitrous

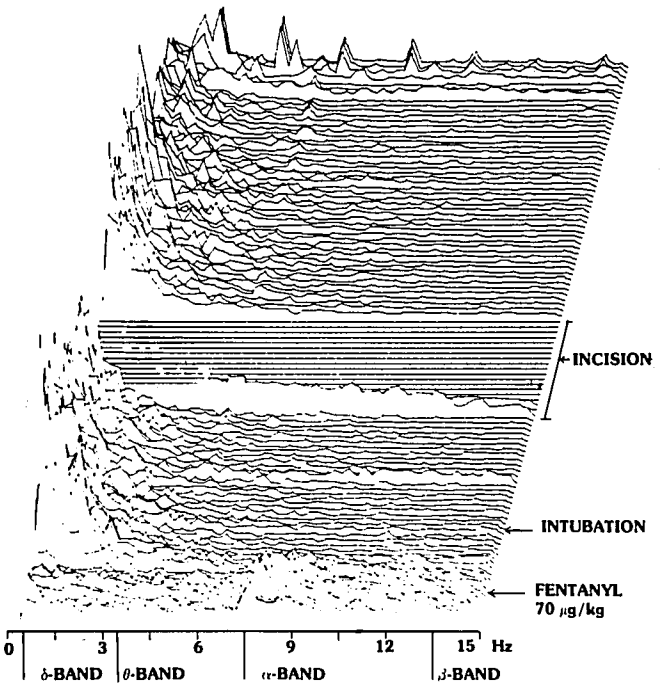

FIG. 8. Three-dimensional power spectral analysis of a single EEG using $T_4 \rightarrow C_0$ derivation. Lorazepam premedication, fentanyl 70 μg/kg^{-1}, air/O_2. EEG frequency is shown on the horizontal axis, time is shown going upwards and towards the rear. EEG amplitude (μV) is shown on the vertical axis. Each line represents 50 s in time.

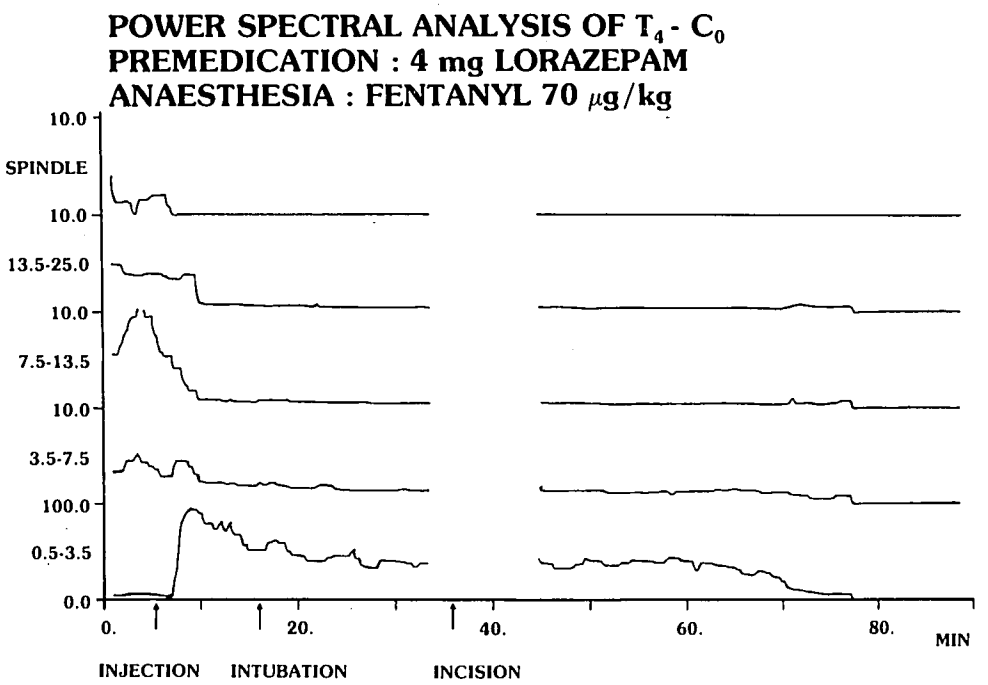

FIG. 9. Wide band spectral analysis of the same EEG as figure 8. On the vertical axis power (μV^2) is shown (scale 0–10 or 0–100). The EEG frequencies are delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–13.5 Hz), beta (13.5–25.0), and spindles (10–14 Hz).

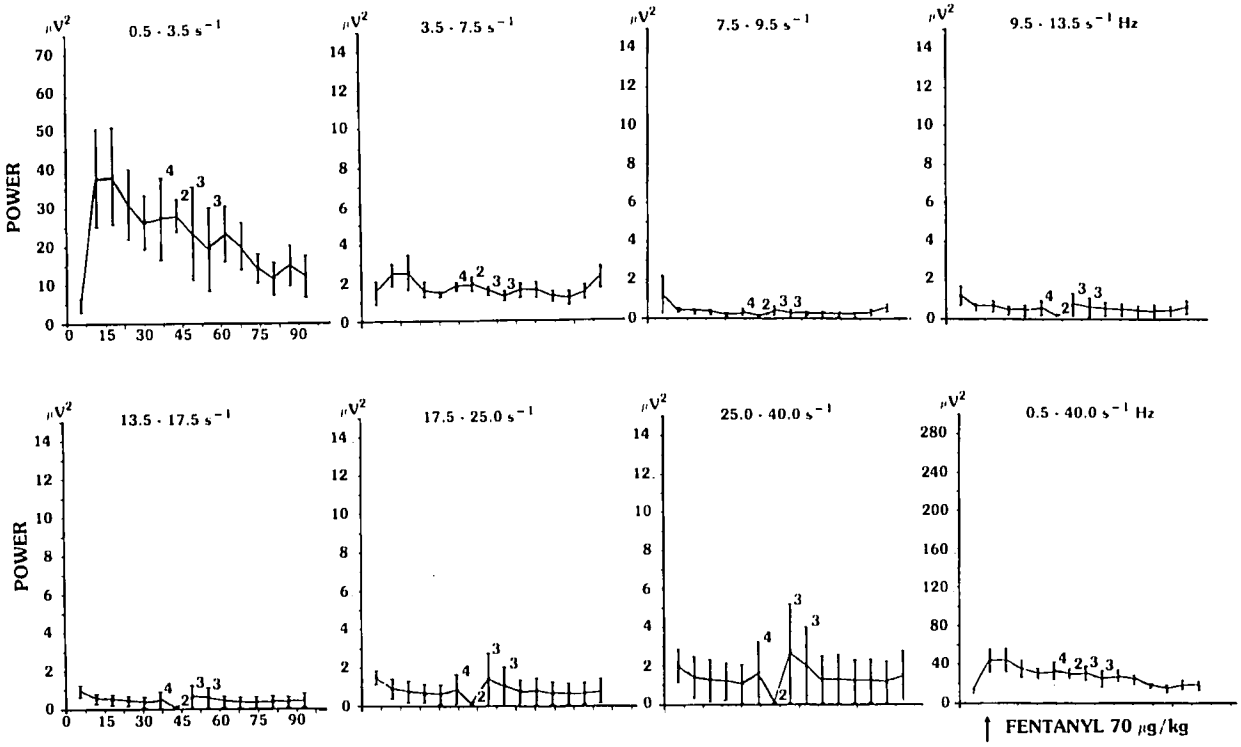

FIG. 10. Mean power (±SD) for five patients (lorazepam, fentanyl 70 μg/kg, air/O_2) in the following frequency bands: delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), $alpha_1$ (7.5–9.5 Hz), $alpha_2$ (9.5–13.5 Hz), $beta_1$ (13.5–17.5 Hz), $beta_2$ (17.5–25.0 Hz), $beta_3$ (25.0–40.0 Hz) and total power. Time in minutes is shown on the vertical axis. The small numbers indicate analysis used from reduced numbers of patients owing to diathermy artifact.

oxide does not alter the EEG responses to fentanyl. We speculate that fentanyl acts on central and/or peripheral opiate receptors and this action is not affected or potentiated by 50 per cent nitrous oxide. As all patients were unaware, nitrous oxide does not appear to be a necessary component of narcotic anesthesia in premedicated patients.

Kugler *et al.*[13] have studied the EEG changes in human volunteers after fentanyl, 2 μg/kg, and found EEG levels to B_0 using his classification.[6] St. Kubicki *et al.*[14] studied fentanyl up to a total of 0.5 mg per patient during neurolept analgesia with droperidol and 70 per cent nitrous oxide and described high-voltage delta waves. This is similar to the response seen in our series with much larger doses of fentanyl used as a complete anesthetic agent.

The EEG pattern seen after fentanyl is not dissimilar from a normal sleep progression. Spindle activity occurs after fentanyl but K complexes are not seen. These are both features of a normal sleep EEG. Fentanyl anesthesia is characterized by increasing delta activity. Any similarity in EEG response between fentanyl and sleep does not mean that fentanyl anesthesia is in any way related to the physiologic state of sleep. It is not possible to rouse a patient from fentanyl anesthesia and the duration of anesthesia is limited by the elimination of fentanyl from the body.

In the patient in the 30 μg/kg fentanyl group who was given a fentanyl supplement before bypass, the EEG level became lighter coincident with conventional signs of light anesthesia. The EEG may give an indication that anesthesia is becoming "light" and provide a guide for the need to supplement anesthesia, this should not, however, replace normal clinical considerations.

In this study, the EEGs were only analyzed retrospectively and in this one instance would have given an early indication that anesthesia was becoming "light". The value of the EEG as a guide to depth during fentanyl anesthesia requires further investigation. To use the raw EEG as such a guide would require the continual presence of a trained observer, but the use of on-line computer analysis may make this a more feasible proposition.

Because fentanyl anesthesia causes minimal changes in hemodynamics,[4,5] a view borne out by this study, the EEG changes observed are not related to changes in cardiovascular parameters. It is therefore not possible to correlate hemodynamics with EEG levels.

Fentanyl in a dose of 50–70 μgkg produced satisfactory depression of the EEG until the onset of cardiopulmonary bypass. Bypass with moderate hypothermia (24°C) produced profound EEG changes rendering it unsuitable for analysis. There were no

TABLE 3. Cardiovascular Data

	Before Induction	After Induction	After Incision	After Sternotomy
Fentanyl (30 μg/kg)				
Systolic pressure (torr)	142 ± 9.70	116 ± 9.27*	124 ± 5.10	172 ± 8.00*
Diastolic pressure (torr)	79 ± 3.32	69 ± 6.40	78 ± 4.99	83 ± 5.70
Heart rate (beats/min)	64 ± 1.00	66 ± 2.52	62 ± 2.18	84 ± 5.33*
Fentanyl (50 μg/kg)				
Systolic pressure (torr)	142 ± 8.00	130 ± 8.37	140 ± 10.95	156 ± 11.66
Diastolic pressure (torr)	76 ± 3.67	67 ± 3.00	79 ± 6.60	80 ± 3.54
Heart rate (beats/min)	68 ± 4.60	62 ± 3.09	63 ± 4.63	68 ± 6.04
Fentanyl (60 μg/kg)–N_2O				
Systolic pressure (torr)	134 ± 6.78	124 ± 11.22	130 ± 11.40	153 ± 11.57
Diastolic pressure (torr)	80 ± 2.74	74 ± 5.09	77 ± 6.04	90 ± 7.24
Heart rate (beats/min)	76 ± 6.17	65 ± 4.74	68 ± 3.40	72 ± 3.44
Fentanyl (60 μg/kg)–Air				
Systolic pressure (torr)	141 ± 6.31	135 ± 6.87	137 ± 4.40	149 ± 5.92
Diastolic pressure (torr)	75 ± 3.77	78 ± 4.07	71 ± 2.68	77 ± 4.11
Heart rate (beats/min)	78 ± 4.94	82 ± 5.39	81 ± 3.82	89 ± 5.76
Fentanyl (70 μg/kg)				
Systolic pressure (torr)	132 ± 6.80	124 ± 7.52	136 ± 6.36	155 ± 9.10
Diastolic pressure (torr)	67 ± 2.14	67 ± 2.71	71 ± 2.47	82 ± 3.89*
Heart rate (beats/min)	82 ± 5.74	80 ± 7.00	78 ± 5.27	81 ± 5.87

*$P < 0.01$ compared with before induction value.

EEG responses observed to any anesthetic or surgical stimulus and all patients were unconscious.

It is important with any anesthetic technique to ascertain that patients have no awareness during the operative procedure. That sporadic episodes of awareness occur during morphine anesthesia is a disadvantage of that technique.[3] In our study, no patient reported awareness during any part of the procedure following direct questioning. Lorazepam used as premedication has an amnesic effect of its own as evidenced by the fact that few patients who received lorazepam could remember having catheters put in under local anesthesia. For this reason, we studied a group of nine patients who received morphine, a sedative drug with unreliable amnesic properties, as premedication. None of these patients had any recall of events after pre-oxygenation. Although data from this study suggest that premedicated patients have amnesia for the operative procedure following fentanyl anesthesia, the numbers are small. Further large scale investigations are necessary to confirm or disprove this observation. We considered it unethical to study the effects of fentanyl in the absence of any premedication and cannot make any predictions about the effects of fentanyl when given alone.

We therefore conclude that anesthesia with fentanyl produces a characteristic EEG response and that combined with appropriate premedication is a suitable drug for providing unconsciousness, analgesia, and amnesia during cardiac surgery.

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