

## Induction of Anesthesia with Small Doses of Sufentanil or Fentanyl: Dose Versus EEG Response, Speed of Onset, and Thiopental Requirement

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The purpose of this study was to examine the dose *versus* EEG response relationship, the speed of onset, and the thiopental requirement for induction of anesthesia with small doses of sufentanil and fentanyl. The power spectrum of the electroencephalogram (EEG) was used to quantify the effect of the opioids. Eighty male surgical patients, 52-80 yr old, were randomly divided into eight groups of ten to receive fentanyl, 5, 7, 10, or 13  $\mu\text{g}/\text{kg}$ , or sufentanil, 0.5, 0.7, 1.0, or 1.3  $\mu\text{g}/\text{kg}$ . The opioid was given iv over 1 min at a constant rate of infusion. Three to four minutes after the start of the opioid dose, thiopental was given iv in 25 mg increments every 30 s until the patient was unconscious. Power in the 1-3 Hz band reached maximum levels in less than 4 min after the start of opioid administration. At fentanyl doses of 7.0  $\mu\text{g}/\text{kg}$  or less, or sufentanil doses of 1.0  $\mu\text{g}/\text{kg}$  or less, the EEG effects did not increase in proportion to the dose of opioid. There was not a significant difference in the maximum power achieved in the 1-3 Hz band for sufentanil, 0.5, 0.7 and 1.0, and fentanyl, 5 and 7  $\mu\text{g}/\text{kg}$ . Doses of fentanyl, 10 or 13  $\mu\text{g}/\text{kg}$ , or sufentanil, 1.3  $\mu\text{g}/\text{kg}$  were substantially more effective; the maximum power increased significantly between 7 and 10  $\mu\text{g}/\text{kg}$  of fentanyl and 1.0 and 1.3  $\mu\text{g}/\text{kg}$  of sufentanil ( $P < 0.0001$ ). The potency of sufentanil and fentanyl were compared by superimposing, the dose *versus* response (power) curves. The potency ratio was 1:8 (sufentanil:fentanyl). Speed of onset (T50) was determined from the time required to reach 50% of the maximum power in the 1-3 Hz band. Mean T50 was similar for sufentanil, 0.5, 0.7, and 1.0  $\mu\text{g}/\text{kg}$  ( $132 \pm 21$  s, including the 60 s drug injection) and fentanyl, 5 and 7  $\mu\text{g}/\text{kg}$  ( $132 \pm 20$  s). Mean T50 was significantly less ( $P < 0.0001$ ) for sufentanil, 1.3  $\mu\text{g}/\text{kg}$  ( $92 \pm 22$  s) compared with that following an equipotent dose of fentanyl, 10  $\mu\text{g}/\text{kg}$  ( $112 \pm 18$  s). The thiopental dose requirement was inversely related to the dose of opioid and was less for sufentanil compared with fentanyl. Nine of ten patients receiving 1.3  $\mu\text{g}/\text{kg}$  sufentanil did not require thiopental to produce unconsciousness. (Key words: Anesthetics, intravenous: fentanyl; sufentanil; thiopental. Monitoring: electroencephalogram.)

A SMALL DOSE of fentanyl or sufentanil in combination with other drugs, such as thiopental, etomidate, or a benzodiazepine may be used for induction of anesthesia. Even relatively small doses of fentanyl or sufentanil appear to enhance hemodynamic stability during induction, laryn-

gосcopy, and intubation.<sup>1-3</sup> Also, an opioid reduces the dose of thiopental required to produce unconsciousness.<sup>3</sup> However, several fundamental aspects of induction with opioids have not been completely characterized. A dose-response relationship has not been determined; previous studies have examined only a few discrete doses.<sup>1-3</sup> The time course of opioid effects has been reported for continuous infusion<sup>4,5</sup> and for single bolus doses of sufentanil (125  $\mu\text{g}$ ) and fentanyl (1,250  $\mu\text{g}$ ).<sup>6</sup> However, the time at which the maximum effect occurs has not been determined for a range of bolus doses. The thiopental requirement to produce unresponsiveness after opioid administration has not been determined except for two doses of sufentanil (0.5 and 1.0  $\mu\text{g}/\text{kg}$ ).<sup>3</sup> The purpose of this study was to examine the dose *versus* response relationship, speed of onset, and thiopental requirement for a range of small doses of sufentanil and fentanyl, given for induction of anesthesia.

The EEG provides a convenient, noninvasive, continuous measurement of opioid effect that can be used to compare the clinical pharmacology of these drugs. Fentanyl and sufentanil produce a characteristic effect on the electroencephalogram (EEG), which is closely related to the opioid dose and the opioid plasma concentration.<sup>4-8</sup> During an infusion of an opioid the EEG slows progressively as the plasma concentration of the opioid rises.<sup>4,5</sup> EEG activity in the delta frequency band ( $<4$  Hz) appears to be sensitive for measuring the opioid drug effect.<sup>8</sup> Delta activity is normally minimal in the awake state but becomes prominent in response to moderate doses of fentanyl or sufentanil. The relationship of EEG slowing to other drug actions, such as respiratory depression and cardiovascular effects, has not yet been carefully defined.

We have examined the effect of a range of doses of fentanyl (5, 7, 10, and 13  $\mu\text{g}/\text{kg}$ ) and sufentanil (0.5, 0.7, 1.0, and 1.3  $\mu\text{g}/\text{kg}$ ) on the EEG. The magnitude of activity in the 1-3 Hz band and the speed of onset of slowing was used as the measure of drug effect. The dose of thiopental required to produce unconsciousness after each dose of opioid was also determined.

### Methods

Eighty male surgical patients gave institutionally approved and informed consent. Patients with a history of preoperative narcotic or sedative-hypnotic drug use, al-

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TABLE 1. Results (mean  $\pm$  SD)

| Dose ( $\mu$ g/kg) | N  | Age (yr)        | Weight (kg)     | Baseline Power (pW; 1-3 Hz) | Maximum Power (pW; 1-3 Hz) | T50 Time to 50% Maximum Power (s) | Thiopental Dose (mg) |
|--------------------|----|-----------------|-----------------|-----------------------------|----------------------------|-----------------------------------|----------------------|
| <b>Fentanyl</b>    |    |                 |                 |                             |                            |                                   |                      |
| 5                  | 10 | 59.9 $\pm$ 5.0  | 77.3 $\pm$ 13.1 | 3.6 $\pm$ 2.2               | 79.3 $\pm$ 113.6           | 132 $\pm$ 24                      | 137 $\pm$ 82.7       |
| 7                  | 10 | 62.6 $\pm$ 5.1  | 79.9 $\pm$ 8.6  | 4.0 $\pm$ 3.8               | 80.3 $\pm$ 104.2           | 128 $\pm$ 16                      | 81.2 $\pm$ 32.0      |
| 10                 | 10 | 63.4 $\pm$ 7.0  | 87.5 $\pm$ 13.3 | 3.1 $\pm$ 2.2               | 156.8 $\pm$ 66.5†          | 112 $\pm$ 18‡                     | 61.1 $\pm$ 35.6      |
| 13                 | 10 | 69.7 $\pm$ 5.9* | 80.1 $\pm$ 14.5 | 3.5 $\pm$ 1.0               | 253.7 $\pm$ 67.6†          | 92 $\pm$ 18‡                      | 55.0 $\pm$ 38.7      |
| <b>Sufentanil</b>  |    |                 |                 |                             |                            |                                   |                      |
| 0.5                | 10 | 64.7 $\pm$ 6.1  | 78.2 $\pm$ 11.2 | 4.5 $\pm$ 3.0               | 99.5 $\pm$ 73.6            | 132 $\pm$ 31                      | 96.9 $\pm$ 85.0      |
| 0.7                | 10 | 63.7 $\pm$ 4.4  | 78.4 $\pm$ 9.1  | 3.8 $\pm$ 2.4               | 130.6 $\pm$ 81.5           | 132 $\pm$ 16                      | 79.2 $\pm$ 18.8¶     |
| 1.0                | 10 | 62.7 $\pm$ 6.1  | 71.6 $\pm$ 10.2 | 2.6 $\pm$ 2.4               | 95.6 $\pm$ 55.0            | 132 $\pm$ 16                      | 88.9 $\pm$ 33.3      |
| 1.3                | 10 | 63.4 $\pm$ 6.5  | 79.8 $\pm$ 6.5  | 3.6 $\pm$ 2.3               | 167.6 $\pm$ 77.8†          | 92 $\pm$ 22‡§                     | 5.0 $\pm$ 15.8¶      |

\* ANOVA  $P < 0.0001$ ; fentanyl, 13  $\mu$ g/kg, different from other groups.

† ANOVA  $P < 0.0001$ ; fentanyl, 10 and 13  $\mu$ g/kg, and sufentanil, 1.3  $\mu$ g/kg were different from other dose groups.

‡ ANOVA  $P < 0.0001$ ; sufentanil, 1.3  $\mu$ g/kg, and fentanyl, 10 and 13  $\mu$ g/kg, were different from other dose groups.

§ ANOVA  $P < 0.0001$ ; sufentanil, 1.3  $\mu$ g/kg, was faster than an equipotent dose of fentanyl, 10  $\mu$ g/kg.

¶ ANOVA  $P < 0.0001$ ; sufentanil, 0.7 and 1.3  $\mu$ g/kg, required less thiopental compared with equipotent doses of fentanyl, 5 and 10  $\mu$ g/kg, respectively.

cohol abuse, or severe cardiopulmonary, renal, or hepatic disease were excluded from the study. Patients were randomly divided into eight groups of ten individuals to receive fentanyl, 5, 7, 10, or 13  $\mu$ g/kg, or sufentanil, 0.5, 0.7, 1.0, or 1.3  $\mu$ g/kg. No preoperative anesthetic medications were given. EEG recordings were made with the Neurotrac™ computerized EEG monitor (Interspec). A pair of recording electrodes was placed on each side of the head, in frontal and mastoid areas, and a reference electrode was placed in the mid-frontal area, using the procedure recommended by the manufacturer. Electrode impedance was satisfactory (<5 K ohms), as determined by the impedance subroutine performed by the monitor. The gain of the amplifier was set manually (60  $\mu$ V, peak to peak) and was the same for all patients. The compressed spectral array was displayed on the monitor screen, and power in 4 frequency bands (1-3, 4-7, 8-12, and 13-20 Hz) was recorded continuously by a printer. Epochs of 4 s were used. Metocurine, 2 mg iv, was given while the patient breathed oxygen. Patients were asked to close their eyes to minimize eye movements that cause low frequency artifact. Baseline EEG activity was recorded for several minutes. While the eyes remained closed, the dose of sufentanil or fentanyl was administered iv at a constant rate over a period of 1 min. EEG activity was recorded during the administration of opioid and for an additional 2 min. Three minutes after the start of the opioid administration, thiopental was administered in 25 mg iv increments every 30 s until the patient was unconscious, as judged by absence of response to verbal commands ("take a breath", "open your eyes") and tactile stimulus (eyelid reflex, tap on forehead). Eleven patients were unconscious after receiving the opioid alone and did not receive any thiopental. In 15 of the 40 patients who received the low doses

of fentanyl, 5 or 7  $\mu$ g/kg, or sufentanil, 0.5 or 0.7  $\mu$ g/kg, the power in the 1-3 Hz band did not increase above 20 picowatts (pW), a relatively low intensity of delta activity. The EEG of those 15 patients was recorded for 4 min (instead of 3 min) prior to the administration of thiopental to be sure that the peak opioid effect on the EEG was not missed. Spontaneous ventilation was markedly reduced in some patients. These patients were prompted to breathe by verbal command. The lungs of patients who became completely apneic were not ventilated *via* bag and mask until the EEG recording period was completed. Oxygen saturation was measured by pulse oximetry and did not fall below 95%. Rigidity was not clinically evident during the EEG recording period. Laryngoscopy and intubation were performed following administration of succinylcholine.

EEG data were analyzed in the following manner. Power values in the 1-3 Hz band from the left and right hemispheres were averaged, for each 4 s epoch of the EEG record for a total of 45 epochs. The 3 epochs with the greatest power were averaged to give the maximum power value for each patient. The epoch at which half the maximum power was first reached (T50) was also determined for each patient. Mean results from the eight dose groups were compared by one-way ANOVA with post hoc comparisons by Fisher PLSD (Statview 512+, Brainpower, Calabassas, California).

### Results

Table 1 summarizes the patient characteristics and EEG results. The age of patients ranged from 52 to 80 yr, and weight ranged from 55 to 106 kg. There were no significant differences in mean age or weight between the eight

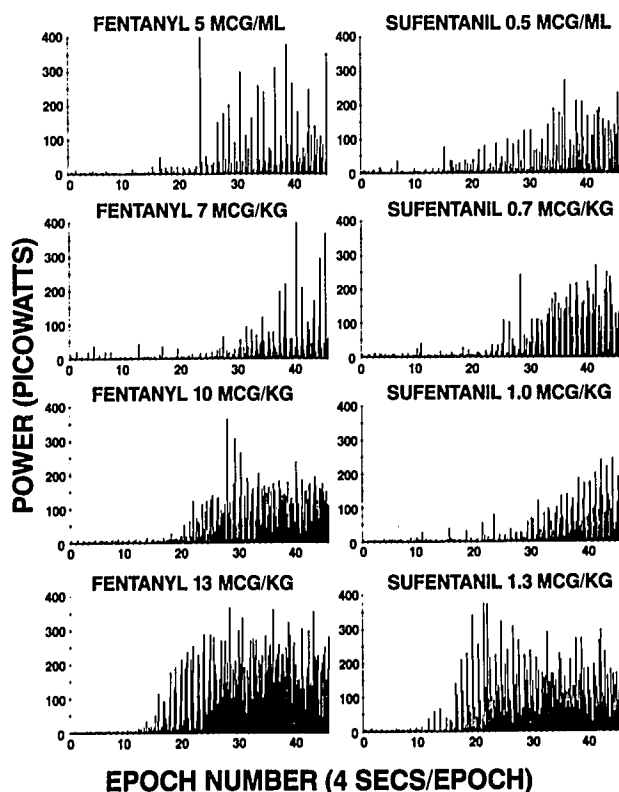


FIG. 1. Power in the 1-3 Hz band is plotted for each patient for each of 45 epochs. Each vertical bar represents the data from one patient. Thus, the data for each epoch is represented by ten bars. Each epoch is 4 s long. The opioid was given iv during the first 15 epochs.

groups of patients except that patients in the fentanyl 13  $\mu\text{g}/\text{kg}$  group were slightly older ( $P < 0.05$ ). Power *versus* time bar graphs for each dose of fentanyl or sufentanil are shown in figure 1. Power reached a maximum level within 3 min of the start of the opioid dose in 78 patients, whereas in the other two patients the maximum was reached within 4 min.

Mean maximum power values (table 1; and fig. 2) were similar for sufentanil, 0.5, 0.7, or 1.0  $\mu\text{g}/\text{kg}$ , and fentanyl, 5 or 7  $\mu\text{g}/\text{kg}$ ; there was not a statistically significant difference between these groups. Doses of fentanyl, 10 or 13  $\mu\text{g}/\text{kg}$ , or sufentanil, 1.3  $\mu\text{g}/\text{kg}$ , resulted in substantially greater mean maximum power values compared with the smaller doses ( $P < 0.0001$ ). The greatest mean maximum power value occurred with fentanyl, 13  $\mu\text{g}/\text{kg}$  ( $P < 0.05$ ). The potency of sufentanil and fentanyl were compared by superimposing the dose *versus* response (power) curves. The potency ratio was 1:8 (sufentanil:fentanyl) when this was performed.

The time required to reach 50% of the maximum power (T50) was similar ( $P > 0.05$ ) for sufentanil, 0.5, 0.7, and 1.0  $\mu\text{g}/\text{kg}$ , and fentanyl, 5 and 7  $\mu\text{g}/\text{kg}$  (table 1; fig. 3). The mean T50 for these dose groups was about 132 s, or approximately 72 s after the end of the 60 s

opioid injection. Maximum power was too low in ten patients (2-28 pW) receiving sufentanil, 0.5 and 0.7  $\mu\text{g}/\text{kg}$ , and fentanyl, 5 and 7  $\mu\text{g}/\text{kg}$ , to clearly distinguish T50 power from baseline power. Data from these patients were not included in the mean T50 values. The proportion of these patients was not significantly different between the dose groups (chi-square  $P > 0.05$ ). The time to T50 was significantly shorter ( $P < 0.0001$ ) for sufentanil, 1.3  $\mu\text{g}/\text{kg}$  ( $92 \pm 21$  s, including the 60 s long opioid injection), and fentanyl, 10 ( $112 \pm 18$  s) and 13  $\mu\text{g}/\text{kg}$  ( $92 \pm 18$  s), compared with that for patients in the lower dose groups. The mean T50 for sufentanil, 1.3  $\mu\text{g}/\text{kg}$ , occurred 20 s earlier than for a nearly equipotent dose of fentanyl, 10  $\mu\text{g}/\text{kg}$  (potency ratio 1:8), a statistically significant difference ( $P < 0.0001$ ).

The relationship between thiopental requirement and opioid dose was plotted (fig. 4), based on a potency ratio of 1:8 for sufentanil and fentanyl. The thiopental requirement was significantly less for sufentanil, 0.7  $\mu\text{g}/\text{kg}$  ( $79 \pm 19$  mg) and 1.3  $\mu\text{g}/\text{kg}$  ( $5.0 \pm 16$  mg), compared with that required with equipotent doses of fentanyl, 5  $\mu\text{g}/\text{kg}$  ( $137 \pm 83$  mg) and 10  $\mu\text{g}/\text{kg}$  ( $89 \pm 33$  mg), respectively ( $P < 0.0001$ ). Only one of ten patients receiving sufentanil, 1.3  $\mu\text{g}/\text{kg}$ , required any thiopental to produce unconsciousness, compared with ten of ten patients re-

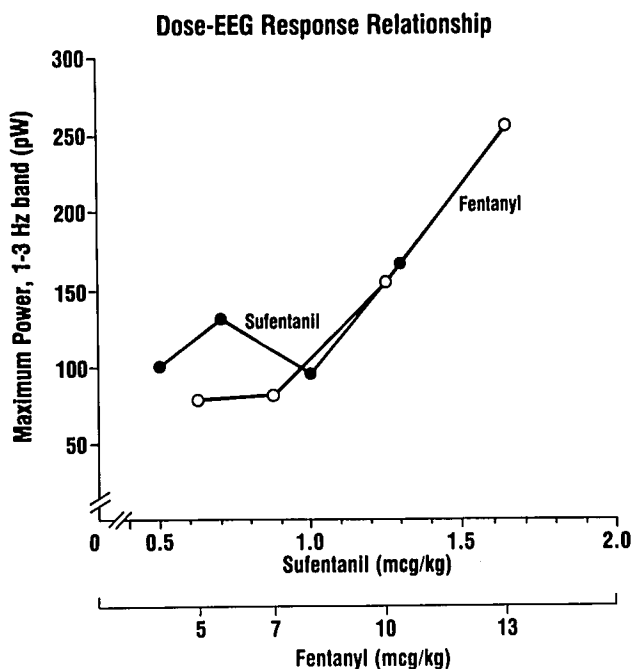


FIG. 2. The maximum power in the 1-3 Hz band was plotted against the opioid dose. Sufentanil and fentanyl doses were plotted to superimpose the dose *versus* response curves as much as possible. The potency ratio was 1:8 (sufentanil:fentanyl). There was not a significant difference in maximum power between sufentanil, 0.5, 0.7, and 1.0  $\mu\text{g}/\text{kg}$  and fentanyl, 5 and 7  $\mu\text{g}/\text{kg}$ . Fentanyl, 10 and 13  $\mu\text{g}/\text{kg}$ , and sufentanil, 1.3  $\mu\text{g}/\text{kg}$ , resulted in substantially greater maximum power compared to the smaller doses ( $P < 0.0001$ ).

ceiving fentanyl, 10 µg/kg, and eight of ten patients receiving fentanyl, 13 µg/kg.

There was a large amount of variation between patients in maximum power and thiopental requirement (table 1). The coefficient of variation (SD/mean × 100%) for maximum power ranged from 42% to 144%, and for the thiopental dose, 32% to 88%.

Hemodynamic effects were not systematically recorded. However, a clinically acceptable degree of hemodynamic stability was found during laryngoscopy and intubation in each of the groups, including the patients who received no thiopental.

### Discussion

Small fentanyl or sufentanil boluses, given for induction of anesthesia, resulted in the rapid onset of EEG slowing. In 78 of the 80 patients the maximum slowing occurred within 2 min following the end of the 1 min opioid injection. The speed of onset of EEG slowing was related to the dose of opioid. At the highest doses of fentanyl and sufentanil tested, T50, or the time of 50% of the maximal slowing, was reached an average of 32 s after the end of the 1 min injection. Cork *et al.* administered fentanyl over a period of 5 min in advance of a rapid sequence induction with thiopental, presumably to allow enough time for the

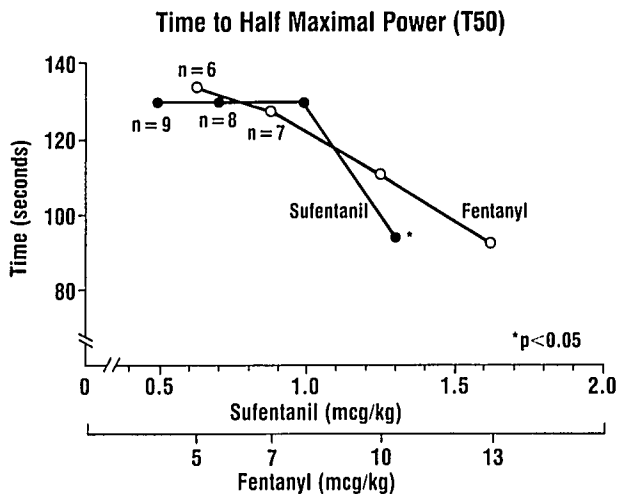


FIG. 3. The time (s) required to reach half of the maximum power (T50) was plotted against the opioid dose. The time includes the 60 s of drug administration. Sufentanil and fentanyl doses were plotted on the same scale, with a potency ratio of 1:8. Maximum power was quite low in ten patients in the dose groups, sufentanil, 0.5 and 0.7 µg/kg, and fentanyl, 5 and 7 µg/kg, so that the T50 power could not be distinguished from baseline power. Data from these patients were not included in the mean T50 values. For those dose groups the number of patients included in the mean T50 are shown on the figure. T50 was significantly shorter ( $P < 0.0001$ ) for sufentanil, 1.3 µg/kg, and fentanyl, 10 and 13 µg/kg, compared to the lower dose groups. T50 for sufentanil, 1.3 µg/kg, was significantly shorter than for an equipotent dose of fentanyl, 10 µg/kg ( $P < 0.0001$ ).

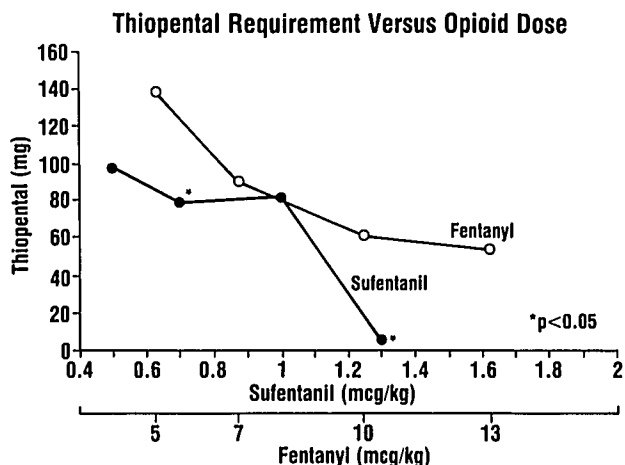


FIG. 4. Thiopental was administered iv in 25 mg increments every 30 s until the patient was unconscious. The thiopental requirement was plotted against the opioid dose. Sufentanil and fentanyl doses were plotted on the same scale, using a potency ratio of 1:8. The thiopental requirement was significantly smaller ( $P < 0.0001$ ) for sufentanil, 0.7 and 1.3 µg/kg, compared to equipotent doses of fentanyl (5 and 10 µg/kg, respectively). Only one of ten patients receiving sufentanil, 1.3 µg/kg, required any thiopental, compared to ten of ten in the fentanyl, 10 µg/kg group and eight of ten in the fentanyl, 13 µg/kg group ( $P < 0.0001$ ).

fentanyl to take effect.<sup>2</sup> Our data suggest that the onset of the larger doses of sufentanil and fentanyl is fast enough and that opioid preloading prior to rapid sequence induction is probably unnecessary. However, further studies will be necessary to determine whether speed of onset of EEG effects corresponds to hemodynamic and other effects.

In this study we compared the potency of sufentanil and fentanyl by attempting to superimpose the dose versus response curves for EEG power in the 1–3 Hz band (fig. 2). The result was a potency ratio of approximately 1:8. Previous studies using both EEG and clinical measures of drug effect have found potency ratios ranging from 1:5 to 1:11.<sup>5,9</sup> The comparison of potency between two opioids is not simple. Potency depends upon a wide variety of factors, including intrinsic activity at the site of action, ability to penetrate tissues and reach the site of action, and pharmacokinetic factors such as volume of distribution and clearance. The ratio between equipotent doses may be different for a bolus compared with that for a continuous infusion because of pharmacokinetic factors.<sup>4</sup> Apparent potency may also vary depending on which drug effect is measured and the technique used to make the measurement. The clinical measurement of opioid effect is complex and difficult to use in dose-response studies in which measurement of drug effect must be made frequently and rapidly. This is one reason for our use of the EEG, a continuous noninvasive measure of opioid drug effect on the brain.

A previous study of the relative speed of onset of sufentanil and fentanyl found that onset of effect with sufentanil was faster,<sup>10</sup> whereas another study found no difference.<sup>5</sup> In this study sufentanil, 1.3  $\mu\text{g}/\text{kg}$ , had a significantly shorter T50 compared with the dose of fentanyl, 10  $\mu\text{g}/\text{kg}$ , which produced nearly the same maximum power. There was not a significant difference in speed of onset between smaller doses of sufentanil and fentanyl. Discrepancies in results from various studies are probably related to differences in dose, rate of administration, and ability to measure drug effects frequently and with precision. Thus, sufentanil appears to be faster in onset than an equipotent dose of fentanyl under certain circumstances but not in all circumstances.

The dose of thiopental required to produce unconsciousness after opioid administration was inversely related to the dose of opioid (fig. 3). The thiopental requirement was small, often less than 1.0 mg/kg. Brizgys *et al.* have determined the thiopental requirement for sufentanil, 0.5 and 1.0  $\mu\text{g}/\text{kg}$ , and obtained results similar to ours.<sup>3</sup> The thiopental requirement was not entirely predictable from the EEG because the fentanyl 13  $\mu\text{g}/\text{kg}$  group had a greater mean maximum power value, but paradoxically, a greater thiopental requirement compared with that for the sufentanil 1.3  $\mu\text{g}/\text{kg}$  group.

Although opioids are not usually considered to be complete anesthetic agents, large doses have been used to produce analgesia, unconsciousness, and amnesia.<sup>11</sup> In this study surprisingly small doses of opioid produced unconsciousness without addition of thiopental in some patients, and these patients had no recall of laryngoscopy and intubation. Only one of ten patients receiving sufentanil, 1.3  $\mu\text{g}/\text{kg}$ , required thiopental (one patient required thiopental, 50 mg), compared with ten of ten patients receiving fentanyl, 10  $\mu\text{g}/\text{kg}$ , and eight of ten patients receiving fentanyl, 13  $\mu\text{g}/\text{kg}$ . Flacke *et al.*<sup>9</sup> also found that sufentanil produced unconsciousness readily. Forty-seven percent of their patients were unconscious after receiving less than 1.5  $\mu\text{g}/\text{kg}$  of sufentanil. The ED<sub>95</sub> for unconsciousness with sufentanil must be small, possibly less than 2  $\mu\text{g}/\text{kg}$ .

There was a large variation in response to the opioids and thiopental between patients. Therefore, the dose of opioid and thiopental must be individualized in the clinical setting. This conclusion is in agreement with previous work by others.<sup>5,8,12</sup> Because the effects of opioids and thiopental vary with age,<sup>12-14</sup> and the patients in this study were older than 50 yr of age, the results may not be directly applicable to younger patients in whom larger doses would probably be needed to obtain the same effects.

Several results of this study may have clinical importance. First, sufentanil and fentanyl act rapidly. Maximum EEG effects occurred less than 2 min after the end of opioid administration in most patients. Second, the thiopental requirement was small and inversely related to

opioid dose; nine of ten patients receiving sufentanil, 1.3  $\mu\text{g}/\text{kg}$ , required no thiopental to produce unconsciousness. Finally, at fentanyl doses of 7  $\mu\text{g}/\text{kg}$  or less, or sufentanil doses of 1.0  $\mu\text{g}/\text{kg}$  or less, EEG effects did not increase in proportion to the dose of opioid. Sufentanil, 1.3  $\mu\text{g}/\text{kg}$ , and fentanyl, 10 and 13  $\mu\text{g}/\text{kg}$ , produced significantly faster, more intense EEG slowing compared with smaller doses of either drug. Therefore, when rapid, profound opioid effects are desired, the larger of these doses should be selected.

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