EEG Quantitation of Narcotic Effect: The Comparative Pharmacodynamics of Fentanyl and Alfentanil

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Fentanyl and alfentanil produce very similar electroencephalographic (EEG) changes in humans. With increasing serum concentrations of either narcotic, progressive slowing in frequency occurs. This narcotic effect on the brain was quantitated using off-line EEG power spectrum analysis. During EEG recording, six unpremedicated patients received a fentanyl infusion (150 µg/min), and six received alfentanil (1,500 µg/min) until a specific level of EEG depression (delta waves) occurred. Timed arterial blood samples were obtained for measurement of the narcotic serum concentrations. The narcotic-induced EEG changes were found to lag behind (in time) the serum narcotic concentration changes. To accurately relate EEG changes to serum narcotic concentrations, a pharmacodynamic model (inhibitory sigmoid E_{max}) was combined with a pharmacokinetic model that incorporated an "effect" compartment. (The effect compartment is the separate pharmacokinetic compartment where drug effect is directly proportional to drug concentration. It is the effect site.) The magnitude of the time lag was quantitated by the half-time of equilibration between serum narcotic concentrations and concentrations in the effect compartment. With fentanyl a significantly greater time lag was present (half-time = 6.4 ± 1.3 min; mean ± SD) than with alfentanil (half-time = 1.1 ± 0.3 min). This difference in time lag between blood concentration and effect may be due to the larger brain–blood partition coefficient for fentanyl. The steady-state serum concentration that caused one-half of the maximal EEG slowing was 6.9 ± 1.5 ng/ml for fentanyl, compared with 520 ± 163 ng/ml for alfentanil. Although fentanyl is reported to have a dose potency approximately seven times that of alfentanil, the steady-state serum concentration potency ratio calculated from this study is approximately 75 to 1. This difference may be explained by alfentanil's smaller initial distribution volume and less time lag between serum concentration changes and changes in effect. (Key words: Analgesics: alfentanil; fentanyl. Brain: electroencephalogram. Pharmacodynamics.)

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NARCOTICS PLAY an important role in clinical anesthesia. They have long been used to supplement general anesthesia and to provide preoperative and postoperative analgesia. In more recent years they have been utilized as the primary anesthetic agent in major surgical procedures.[1-3]

Fentanyl differs from older opioids, such as morphine or meperidine, by having a rapid onset and a short duration of effect when used in low doses.[4] The reported pharmacokinetics of fentanyl differ little from those of morphine and meperidine.[5-7] Alfentanil is a new synthetic narcotic reported to have an even more rapid onset and shorter duration of effect than fentanyl.[8] Compared with fentanyl, its distribution kinetics are similar but it has a shorter elimination half-life due to its smaller volume of distribution at steady-state.[9,10]

The narcotic effects of fentanyl and alfentanil appear to parallel their serum concentrations more closely than do the effects of morphine and meperidine. This potentially makes fentanyl and alfentanil more suitable for controlling the narcotic effect and for achieving greater safety in clinical usage. For low doses, termination of the narcotic effect for fentanyl and alfentanil depends on redistribution mechanisms to lower serum concentrations in a manner analogous to thiopental.[4,11]

Although both fentanyl and alfentanil have fewer cardiovascular side effects than morphine or meperidine, the problems of respiratory depression and postoperative central nervous system depression remain.[12] More scientific use of these narcotics along with the avoidance of underdosing or overdosing could be attained if the anesthesiologists had a sensitive, continuous, noninvasive measure of narcotic effect.

Both fentanil and alfentanil cause a progressive, predictable slowing (fig. 1) of the electroencephalogram (EEG).[13,14] Utilizing these EEG changes we have devel-

oped a continuous, noninvasive method of measuring the effect of fentanyl and alfentanil on the brain by power spectral analysis of the EEG and computation of the spectral edge. Simultaneously obtained narcotic serum concentrations are employed to determine the pharmacokinetic disposition of the narcotic in each patient. These two measurements then are related using pharmacodynamic modeling concepts to provide a method of comparing the pharmacodynamics of fentanyl and alfentanil.

Methods

Twelve healthy (ASA I or ASA II) male patients scheduled for elective surgery involving minimal blood loss gave informed consent after Institutional Review Board approval was obtained. All patients were free of significant obesity, or cardiovascular, neurologic, hepatic, renal, or pulmonary disease. None had a history of alcohol or drug abuse.

Each patient was brought unpremedicated to the operating room. An iv catheter was placed in an arm vein for drug administration, and a 20-gauge radial arterial catheter was placed in the contralateral arm for hemodynamic measurements and blood sampling. Five electrodes were placed on the scalp in the following configuration: FP_1-O_1, FP_2-O_2, Cz-O_1, Cz-O_2 (international 10–20 system of electrode placement: FP = frontoparietal region; O = occipital,; Cz = vertex of head; 1 = left side; 2 = right side).[15] A ground electrode also was placed on the forehead in the midline. A Beckman Accutrace® was used to display the EEG, which was recorded on FM magnetic tape with a Vetters Model A® tape recorder for subsequent off-line power spectral analysis. Standard ECG monitoring of lead II was performed. Blood pressure and heart rate were continuously displayed and recorded at 30-s intervals throughout the study.

Glycopyrrolate, 0.2 mg, and pancuronium, 1 mg, were administered iv prior to narcotic infusion to prevent or attenuate bradycardia or chest wall rigidity. A mask was applied lightly to the patient's face and O_2 delivered at 5 l/min via a nonrebreathing system. After a 5-min baseline EEG recording with the patients resting quietly (eyes closed), an iv narcotic infusion was started. Fentanyl was delivered at a rate of 150 μg/min and alfentanil at 1,500 μg/min. Patient responsiveness to verbal commands was assessed approximately every 15 s (commands to move toes or fingers). As soon as a patient failed to respond to a verbal command, a succinylcholine infusion was begun at approximately 1 mg/min to attenuate or eliminate chest wall rigidity and EMG artifacts in the EEG. Ventilation was monitored by precordial stethoscope and visual observations. It was assisted as needed
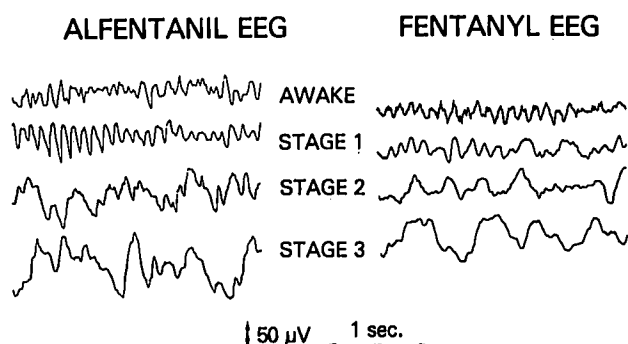
ALFENTANIL EEG   FENTANYL EEG

FIG. 1. EEG Stages for fentanyl and alfentanil. Awake—mixed alpha (8–13 Hz) and beta (>13 Hz) activity. Stage 1—slowing with alpha spindles. Stage 2—more slowing, theta activity present (4–7 Hz). Stage 3—maximal slowing, delta waves present (<4 Hz) with high amplitude.

to maintain clinically adequate ventilation, which was checked by arterial blood gas sampled within 2 min of termination of the narcotic infusion. The infusion for each patient was terminated as soon as evidence of delta wave activity appeared in the EEG (Stage III, fig. 1)—defined as wave of $\leq$4 Hz and an amplitude $\geq$ 50μV. The succinylcholine infusion was stopped when the delta waves began to disappear from the EEG. EEG recording was continued until the patient was alert, and the EEG signal had returned to baseline.

After termination of the EEG recording, patients were anesthetized with thiopental, succinylcholine, nitrous oxide/oxygen, and enflurane for the surgical procedure.

Arterial blood samples (4 ml) were drawn at 0.5- to 1-min intervals during the narcotic infusion and at 2- to 4-min intervals thereafter until the EEG had returned to baseline. Approximately 25 samples were obtained per patient. Each sample was allowed to clot, then promptly centrifuged, and the serum separated and frozen at −20°C until analyzed by radioimmunoassay for serum narcotic concentration.[16,17]

DATA ANALYSIS

The EEG stored on FM magnetic tape was subjected to off-line analysis using a Digital® PDP 11/23 computer. The signal was divided into 5.12-s epochs and digitized at a rate of 200 Hz with 10-bit resolution. These data then were subjected to a fast Fourier transformation to obtain power (amplitude^2) versus frequency histograms for each epoch (fig. 2).[18] For each epoch the spectral edge then was determined by calculating the area under the power versus frequency histogram and finding which frequency had 95% of the area in the histogram below it.[19] Thus, the spectral edge characterizes the degree of slowing for each epoch. The noise in the spectral edge
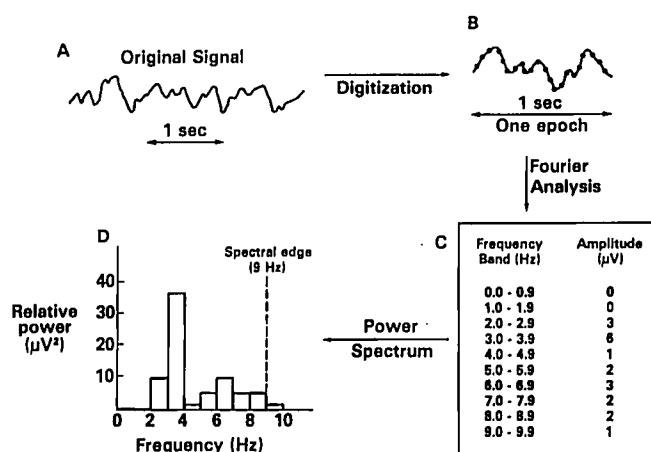
FIG. 2. A schematic representation of the process of power spectrum analysis. The original continuous waveform (A) is put in digital form by sampling it repeatedly at small intervals. One epoch of these data (B) then is passed to a computer program to perform a Fourier analysis. The result of this analysis, shown in C, is a table giving the amplitude of the activity in each frequency band. Finally, the amplitudes are squared (to give power) and plotted as a histogram (D). The spectral edge is that frequency (here 9 Hz), that has 95% of the area in the histogram to its left. Modified from Levy *et al.* Automated EEG processing for intra-operative monitoring. ANESTHESIOLOGY 53:223–236, 1980, with permission of the publisher.

data was decreased by a curve-smoothing technique that represents each spectral edge value by the mean of 5 previous and 5 following spectral edge values. Thus, each spectral value is the moving arithmetic mean of 51.2 s (10 epochs) of signal.

The spectral edge data then were related to fentanyl or alfentanil plasma concentration data using nonlinear regression[20] and the following pharmacodynamic (inhibitory sigmoid E_{max}) model[21]:

$$SE_{(t)} = E_o - E_{max} \cdot Ce_{(t)}^{\gamma}/[IC_{50}^{\gamma} + Ce_{(t)}^{\gamma}]$$

Where $SE_{(t)}$ is the spectral edge (Hz) at time t; E_o is the baseline spectral edge (Hz); E_{max} is the maximal decrease in spectral edge (Hz) produced by the narcotic; IC_{50} is the steady-state fentanyl or alfentanil concentration (ng/ml) that produces 50% of the maximal decrease in spectral edge; γ is a dimensionless number reflecting the sigmoidicity of the curve; and $Ce_{(t)}$ is the concentration of the narcotic (ng/ml) in the effect compartment at time t.

Because of the temporal lag (or hysteresis) between changes in serum narcotic concentration and changes in spectral edge, the spectral edge data could not be related directly to serum concentrations. Instead, the above pharmacodynamic model was coupled with a pharmacokinetic model that postulates a separate "effect" compartment.[22] The effect compartment is the site

where the drug exerts its effect. The effect produced (here spectral edge changes) is linked directly to the concentration in the effect compartment and how the concentrations in the effect compartment translate into effects is dictated by the pharmacodynamic model. A first-order rate constant (K_{eo}) characterizes the temporal aspects of equilibration between the effect compartment concentration and the serum concentration. Thus, $T\frac{1}{2} K_{eo}$ (0.693/K_{eo}) is the half-time for equilibration between serum concentration and effect compartment concentration, and it quantitates the magnitude of the temporal lag or hysteresis.

The ages, weights, heights, and total dose received as well as the pharmacodynamic parameter estimates for fentanyl and alfentanil were compared using an unpaired *t*-test. A P value of <0.05 was considered statistically significant.

Results

The patients receiving fentanyl or alfentanil did not differ statistically in age, weight, or height, and they underwent similar surgical procedures. The total dose required to produce delta waves in the EEG ranged from 600 to 825 μg for fentanyl and from 6,000 to 9,000 μg for alfentanil (table 1). The alfentanil dose was approximately 10 times the fentanyl dose.

With the fentanyl infusion, the clinically detectable onset of respiratory depression occurred in each patient after 3–5 min and preceded loss of consciousness (absent verbal responsiveness) by 30 to 60 s. No patient had clinically significant chest wall rigidity due to the succinylcholine infusion, and ventilation was assisted easily and EMG artifacts were avoided. The period of profound respiratory depression requiring assisted ventilation lasted 10–15 min after termination of the fentanyl and succinylcholine infusions. Clinically, alfentanil differed from fentanyl. After initiation of the alfentanil infusion, the onset of respiratory depression occurred in 1–2 min. The transition from the beginning of respiratory depression to profound respiratory depression (often <1 min) was more rapid than with fentanyl. Unconsciousness occurred almost simultaneously with the onset of apnea. Adequate, spontaneous ventilation returned more rapidly with alfentanil (5–10 min) after termination of the alfentanil and succinylcholine infusions.

Hemodynamics were stable throughout the period of study in both groups of patients. No significant bradycardia or hypotension occurred. With the use of succinylcholine, assisted ventilation was technically easy to administer and was adequate in all patients, since Pa_{CO_2} values drawn during the period of peak respiratory depression were normal (Pa_{CO_2} 35–45 mmHg).

Both fentanyl and alfentanil caused similar EEG

TABLE 1. Patient Demographics

Fentanyl						Alfentanil					
Patient	Age (yr)	Ht (cm)	Wt (kg)	Total Dose (µg)	Operation	Patient	Age (yr)	Ht (cm)	Wt (kg)	Total Dose (µg)	Operation
1	57	178	77	675	Lumbar laminectomy	1	33	180	86	6,000	Vasovasotomy
2	56	178	98	825	Lumbar laminectomy	2	61	178	84	7,500	Lobectomy
3	67	187	104	750	Hardware removal from scapula	3	51	175	76	9,000	Herniorrhaphy
4	64	183	73	750	Femoral–popliteal bypass	4	29	188	95	6,000	Hardware removal from ankle
5	57	180	87	825	Herniorrhaphy	5	66	178	85	7,500	Open lung biopsy
6	51	175	90	600	RTV placement in orbit	6	51	180	83	6,750	Resection chest wall mass
Mean SD	59 ± 6	180 ± 4	88 ± 12	737 ± 88*		Mean SD	49 ± 15	179 ± 4	85 ± 6	7,125 ± 1,137*	

* Significantly different ($P < 0.001$).

changes (fig. 1), namely progressive slowing in frequency and increases in amplitude. The maximal EEG change produced by both drugs was characterized by delta waves of slow frequency (<4 Hz) and large amplitude (>50 μV). Even though the infusion was terminated when delta waves first were seen in the EEG with the fentanyl, we observed in every patient an additional progressive slowing and further decrease in spectral edge over the next several minutes. There was a distinct time lag between peak fentanyl concentration and peak spectral edge changes (fig. 3). The spectral edge changes paralleled the fentanyl concentrations, but with a temporal shift. After reaching the peak of the EEG slowing, the spectral edge gradually returned to baseline over the next 20–30 min. The hysteresis seen with alfentanil was considerably smaller (fig. 4). The delta wave activity seen with alfentanil infusion did not progress after

termination of the infusion. The return to baseline occurred more rapidly with alfentanil.

The relationship between spectral edge and serum narcotic concentration forms a hysteresis loop (fig. 5). Each loop has two parts: a curve of spectral edge *versus* increasing serum concentration and a second curve of spectral edge *versus* decreasing serum concentration. Thus, each spectral edge value is associated with two different serum narcotic concentrations (*i.e.*, hysteresis). One also can consider each loop as consisting of two concentration–response curves. If *no* hysteresis were present, the two component curves would be indistinguishable. Since no time element is present, the magnitude of the hysteresis ($T\frac{1}{2}$ K_{eo}) cannot be determined from these graphs. The ability of the inhibitory sigmoid E_{max} model to characterize the spectral edge *versus*
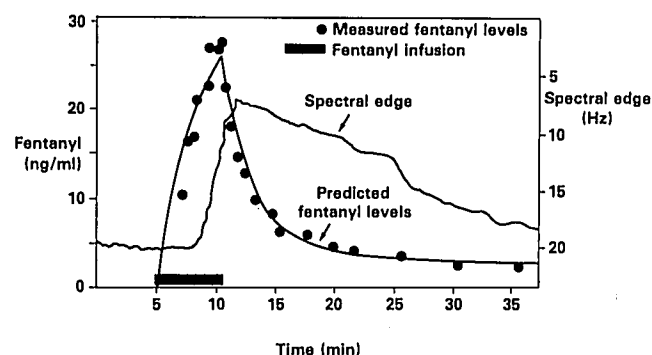

FIG. 3. Time course of spectral edge and serum fentanyl concentrations. Note the inverted spectral edge axis. The spectral edge changes lag behind the serum concentrations changes. Fentanyl infusion rate = 150 μg/min (solid bar).
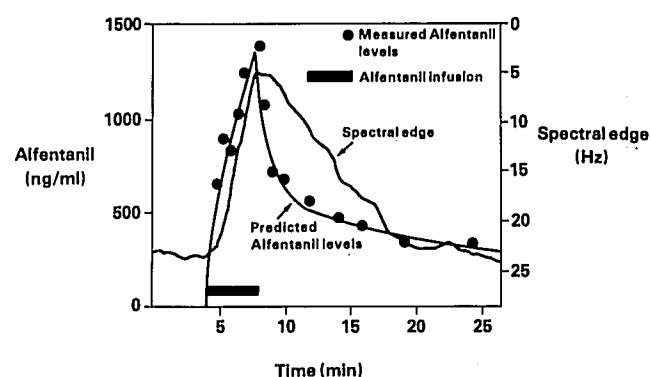

FIG. 4. Time course of spectral edge and serum alfentanil concentrations. Note the inverted spectral edge axis. Spectral edge changes closely parallel serum concentrations. Alfentanil infusion rate = 1500 μg/min (solid bar).
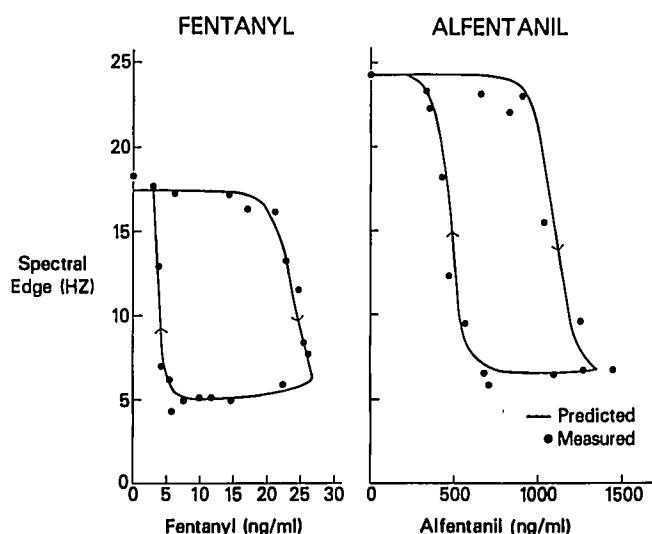
FIG. 5. Spectral edge *versus* serum concentration. Note that no time reference is present in the plots. The same spectral edge is achieved at two different narcotic serum concentrations. The values change in a clockwise manner, as indicated by the arrows on the predicted line.

narcotic serum concentration relationship can be seen from the close approximation of the fitted function (solid line) to the data points (fig. 5).

The estimated pharmacodynamic parameters values for E_o, E_{max}, and γ do not differ statistically between fentanyl and alfentanil patients (table 2). The IC_{50} values, however, are statistically different, reflecting a difference in concentration needed to cause a defined degree of EEG slowing. The alfentanil IC_{50} is approximately 75 times greater than that of fentanyl. The degree of hysteresis quantitated by $T\frac{1}{2} K_{eo}$ is significantly greater for fentanyl than for alfentanil.

Discussion

The pharmacokinetic differences between fentanyl and alfentanil have been described previously.[10] Com-

pared with fentanyl, alfentanil has a smaller initial distribution volume (V_1), a smaller distribution volume at steady state (Vd_{ss}), a lower clearance, and a shorter terminal elimination half-life. The distribution phase kinetics appear to be similar for the two narcotics. At low doses both narcotics have a redistribution mechanism that terminates the narcotic effect. These pharmacokinetic considerations do not explain why alfentanil has a more rapid onset and dissipation of narcotic effect. The shorter elimination half-life would only explain more rapid recovery after large doses or steady state conditions.[9]

Our ability to use a pharmacodynamic model to characterize accurately the relationship between the narcotic serum concentration and drug effect (EEG slowing) has provided new insight into the clinical differences between fentanyl and alfentanil. A significant difference in the degree of temporal lag or hysteresis was found with fentanyl compared with alfentanil. Previous reports on these narcotics, hampered by the lack of a continuous measurement of drug effect, have not examined closely the relative time of onset of drug effect. Other methods of measuring narcotic effect are discontinuous and infrequent (*e.g.*, CO_2 response testing) or require patient alertness and cooperation (*e.g.*, analgesia testing). During the time it takes to make these measurements, the narcotic concentrations in blood are often unknown or rapidly changing, making interpretation difficult. In addition, the method of drug administration will affect the time of onset of drug effect. Bolus injections that rapidly achieve high concentrations in blood will interfere with the detection of any temporal lag. Our study design, using a rapid infusion rate, was well suited for detecting differences in the time of onset of effect and in the relationship between serum concentration and effect.

There are four physiologic and physicochemical reasons for a narcotic to exhibit hysteresis between the serum concentration and drug brain effect.[22] They are

TABLE 2. Pharmacodynamic Parameter Estimates

	Fentanyl					Alfentanil				
Patient	T½ Keo (min)	E_o (Hz)	E_{max} (Hz)	γ (—)	IC_{50} (ng/ml)	Patient	T½ Keo (min)	E_o (Hz)	E_{max} (Hz)	γ (—)	IC_{50} (ng/ml)
1	4.6	17.4	12.9	5.2	6.3	1	1.4	24.3	18.3	6.6	563
2	8.5	22.2	15.2	5.8	5.9	2	0.9	14.5	9.4	4.9	675
3	7.0	18.3	14.0	3.9	6.2	3	1.0	18.8	13.7	5.4	716
4	6.8	18.8	11.2	5.8	5.8	4	0.9	22.6	17.4	2.6	478
5	5.6	19.5	16.1	3.3	9.6	5	1.5	19.4	14.9	3.7	289
6	6.1	18.9	15.2	5.2	7.4	6	0.7	20.8	14.5	5.8	401
Mean SD	6.4 ± 1.3	19.2 ± 1.6	14.1 ± 1.8	4.9 ± 1.0	6.9 ± 1.5	Mean SD	1.1 ± 0.3*	20.1 ± 3.4†	14.7 ± 3.1†	4.8 ± 1.5†	520 ± 163*

* Statistically significant difference, alfentanil *versus* fentanyl ($P < 0.001$).   † No significant difference.

as follows: 1) perfusion (narcotic delivery to the brain); 2) diffusion (crossing the blood brain barrier and cell membranes to reach opioid receptors); 3) partitioning (nonspecific binding of the narcotic to nonreceptor sites in the CNS); 4) receptor events (affinity, dissociation constants).

It is possible to examine each one of these variables to speculate why fentanyl has more hysteresis than alfentanil. Both drugs have minimal effects on hemodynamics and, presumably, perfusion to the central nervous system (CNS) is the same for both. Diffusion and penetrability of membranes should be related to lipid solubility. Meuldermans *et al.* report fentanyl to be more lipid soluble (octanol:water partition coefficient at pH 7.4: fentanyl 860, alfentanil 130).[23] Although lipid solubility can be a rate-limiting factor in onset of effect (morphine's low lipid solubility[24] and slow penetration of the blood–brain barrier appears to be responsible for its slow onset of effect[25]), it appears that both fentanyl and alfentanil have adequate lipid solubility to allow rapid blood–brain barrier penetration.

Experimental animal studies suggest differences in the blood–brain partitioning for these two narcotics. After bolus iv administration and during the postdistribution phase, fentanyl brain concentrations in rats are approximately five times those in plasma (serum–brain ratio of 1:5).[4] For alfentanil, it is the reverse with a serum–brain ratio of 1:0.2.§ If one assumes no blood–brain barrier diffusion limitations, then these partitioning differences probably are due to solution of the narcotic in lipids and nonspecific tissue binding in the brain at sites other than the opioid receptors.

These partitioning differences suggest that fentanyl has a greater number of nonreceptor "storage" sites in the CNS than alfentanil does. Whether these "storage" sites represent nonspecific tissue binding sites or simply greater solution of the molecule in lipids is not clear. Leysen *et al.*[26] have presented data that fentanyl has less nonspecific binding than alfentanil to purified rat brain membrane preparations. Thus, it is possible that the greater lipid solubility for fentanyl leads to increased solution of fentanyl in CNS lipid, which accounts for the partitioning differences. This situation would result in fentanyl having a larger depot to fill before the concentration of free drug at the receptor sites is adequate to cause a narcotic effect. Alfentanil, with fewer "storage" sites to fill, would be able to achieve a higher concentration of free drug at opioid receptor

sites sooner. This situation is analogous to the alveolar-blood equilibration of nitrous oxide and ethyl ether. Nitrous oxide reaches an equilibrium between the lung and blood faster than ether, which has a high blood solubility.

The clinical significance of narcotic receptor events is poorly understood. Available evidence from experimental animal studies suggests that both narcotics have extremely rapid receptor association and dissociation rate constants.[26] Thus, receptor events do not appear to be a rate-limiting step in onset or dissipation of effect for these narcotics.

Many anesthetic drugs exhibit hysteresis. Hysteresis in narcotic analgesic effects in animals has been reported but not carefully quantitated.[27,28] The degree of hysteresis found with fentanyl is approximately the same magnitude as that seen with the nondepolarizing muscle relaxants ($T\frac{1}{2}$ K_{eo} = 4–7 min),[29] whereas alfentanil's hysteresis resembles that of thiopental ($T\frac{1}{2}$ K_{eo} = 1 min).[30] Fentanyl's significant hysteresis has relevant clinical implications. When using fentanyl during balanced anesthesia, our EEG data suggest that it is necessary to give fentanyl 5–10 min *prior* to a noxious stimulus to guarantee that maximal brain effects will be present when the stimulus occurs. Fentanyl is not as "rapidly acting" as many anesthesiologists consider it to be. The smaller hysteresis makes alfentanil potentially more controllable as effects more closely follow the serum concentrations.[31] For example, if alfentanil is administered by infusion and an increased narcotic effect is required, a small bolus injection and an increase in infusion rate would produce a rapid increase in effect.

The similar values for E_o and E_{max} in both groups are expected because both narcotics cause very similar EEG changes. The γ values seen with both narcotics describe a relatively steep serum concentration–response relationship. Steep concentration–response relationships have been reported for meperidine analgesia.[32] Figure 5 displays the steep nature of the two concentration–response relationships: one during onset of effect (increasing plasma concentrations) and the other during recovery (decreasing plasma concentrations).

The IC_{50} values reflect intrinsic potency differences based on the steady state serum concentrations needed to give a defined EEG effect. Previous reports have estimated that alfentanil is three to 10 times less potent than fentanyl, based upon a bolus iv dose.[11,33] These values did not take into account that hysteresis might be present or that serum concentrations were changing. The IC_{50} is the steady state serum concentration responsible for one-half of the maximal EEG slowing. Therefore, it is a measure of a patient's brain sensitivity to the narcotic under steady state conditions. Our data suggest that alfentanil is 75 times less potent than

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§ Michiels M, Hendricks R, Michielsen L, Heykants J, Lenaerts F: Personal communication. Plasma levels and tissue distribution of alfentanil (R39209) in the male Wistar rat after a single intravenous dose of 0.16 mg/kg. Preclinical Research Report R39209/13, Janssen Pharmaceutica, Beerse, Belgium, January 1981.

fentanyl (alfentanyl IC_{50}/fentanyl IC_{50} = 75:1). A recent article by O'Connor *et al.*[34] reports a 40:1 potency difference between fentanyl and alfentanil, based on analgesia and respiratory depression measurements. The explanation for this large discrepancy in potency between bolus dose data and steady state serum concentration data is probably a pharmacokinetic one. The initial distribution volume (V_1) for alfentanil is approximately five to seven times smaller than fentanyl's V_1 (10.95 l *vs.* 59.70 l).[10] Because of this difference in the initial distribution space, administration of an alfentanil dose seven times larger than a given fentanyl dose will achieve serum concentrations that are approximately 50 times higher than initial fentanyl serum concentrations. The relative lack of hysteresis with alfentanil also leads to a smaller bolus dose requirement because the onset of effect occurs sooner. The potency based upon bolus dose would be identical to steady state concentration potency (IC_{50}) only if the initial distribution volumes and the degree of hysteresis were identical for both drugs.

The possibility of a discrepancy between steady state potency differences and bolus dose potency difference probably occurs more frequently than we may realize. Almost all drugs have some hysteresis between blood concentration and effect if carefully measured. Many experimental designs use bolus injections and report effects based on dose administered without taking into account the possibility of hysteresis or changing blood concentrations. Potency differences reported from experiments that ignore hysteresis or changing blood concentrations should be viewed with some caution.

The IC_{50} values reported here are for narcotic-induced EEG changes. We can think of narcotic effects as a progressive sequence of analgesia, respiratory depression, then EEG slowing as the serum concentration increases. These other measures of narcotic effect presumably will have lower IC_{50} values and may have curves of different shapes. Although little is known regarding the shape of the CO_2 response *versus* narcotic serum concentration curve, some data relating respiratory depression to serum narcotic concentrations are available. For fentanyl, Cartwright *et al.*[35] and Stoeckel *et al.*[36] both report significant respiratory depression associated with fentanil serum concentrations in the range of 2–3 ng/ml. Two recent articles[34,37] associate moderate respiratory depression due to alfentanil concentrations in the range of 100–120 ng/ml. O'Conner *et al.*[34] report that excellent postoperative analgesia is associated with alfentanil concentrations in the range of 10–100 ng/ml. A correlation of analgesia with serum fentanyl concentrations is not available. If respiratory depression, analgesia, or other narcotic effects do prove to parallel

spectral edge changes, then similar temporal patterns might be expected with fentanyl exhibiting more hysteresis.

The noninvasive, continuous measure of narcotic effect that we present here may prove to be a useful tool for investigation of the clinical pharmacology of other narcotics or other drugs, as well as providing insight into the changes in sensitivity to narcotics with aging and various disease states.

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