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Plasma Concentration of Fentanyl, with 70% Nitrous Oxide, to Prevent Movement at Skin Incision

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Background: The Cp50 (minimal steady state plasma concentration of an intravenous analgesic/anesthetic required to prevent a somatic response in 50% of patients following skin incision) and the Cp50-BAR (minimal plasma concentration of an analgesic/anesthetic required to prevent either a somatic, hemodynamic, or autonomic response in 50% of patients following skin incision) have been recently proposed as a measure, like minimum alveolar concentration (MAC; and MAC-BAR), to establish the relative potency of intravenous analgesics. This study was conducted to establish the Cp50 for fentanyl.

Methods: Unpremedicated patients were administered fentanyl (in the presence of 70% N₂O) via computer-assisted continuous infusion, a pharmacokinetic model-driven infusion device. After induction of anesthesia with fentanyl, the randomized target fentanyl concentration was entered into computer-assisted continuous infusion. This target fentanyl concentration was maintained until skin incision. Before induction, prior to skin incision, and immediately after skin incision, arterial blood samples were obtained for measurement of fentanyl and norepinephrine concentrations. At skin incision,

patients were observed for a somatic, hemodynamic, or autonomic response. Only patients in whom the pre- and postincision fentanyl concentrations were within $\pm 30\%$ were included in the calculation of the Cp50. The Cp50 was calculated using logistic regression.

Results: The Cp50 for fentanyl was 3.26 ng/ml, and the Cp50-BAR was 4.17 ng/ml.

Conclusions: Comparing these results with the previously published Cp50 of alfentanil, the potency of fentanyl relative to alfentanil is 1:58. Establishing the Cp50, once effect site equilibration has occurred, will allow pharmacodynamic comparisons between the opioids at equipotent concentrations. (Key words: Analgesics, opioid: fentanyl. Anesthetic techniques: computer-assisted continuous infusion. Anesthetics, intravenous. Potency: Cp50.)

MINIMUM alveolar concentration (MAC) was defined by Eger *et al.*¹ as the minimum steady-state alveolar concentration of an anesthetic at one atmosphere that prevents skeletal muscle movement in 50% of patients or animals in response to a noxious stimulus. Minimum alveolar concentration is an index of potency of the inhalation anesthetics.

A similar index is necessary for intravenous anesthetics. Minimum infusion rate that will prevent movement in response to a surgical stimulus in 50% of patients was proposed as a MAC equivalent value for intravenous anesthetics.² Minimum infusion rate does not ensure either a steady plasma concentration (Cp) or equilibration at the effect site. More recently, Aulsems *et al.*³ determined the Cp of alfentanil that would suppress a response (somatic, hemodynamic, or sympathetic) in 50% of patients to a variety of surgical stimuli. They termed this the Cp50. To define the Cp50 of opioids that exhibit significant kinetic-dynamic dissociation, it is important that equilibration between Cp and effect site occurs before the assessment of response to the given stimulus is made.^{4,5} The same methodology used by Aulsems *et al.* therefore cannot be used to define the Cp50 of fentanyl (or sufentanil) because of the more pronounced hysteresis that exists between their Cp and effect site concentration.^{3,4} Computer-assisted

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continuous infusion (CACI) is a pharmacokinetic model-driven infusion device that enables the delivery of an intravenous drug to a desired and constant concentration.⁶ Maintaining a constant Cp enables equilibration between Cp and the effect site to occur so that a Cp50 can be determined.

We define the Cp50 of fentanyl as the steady-state concentration of the drug (in the presence of 70% N₂O) sufficient to prevent a somatic response to skin incision in 50% of patients. The Cp50 can be regarded as a MAC equivalent. The Cp sufficient to prevent a somatic, autonomic, or hemodynamic response to skin incision in 50% of patients we define as Cp50-BAR (barish autonomic response). The Cp50-BAR can be regarded as a MAC-BAR⁷ equivalent. The aim of this study was to determine the Cp50 and Cp50-BAR for fentanyl.

Materials and Methods

After approval of the Duke Institutional Review Board for human studies and written informed consent were obtained, 22 patients participated in this study. All patients were ASA physical status 1 or 2, between the ages of 18 and 55 yr, and were to undergo either orthopedic or gynecologic surgery. Patients with a history of chronic alcohol or opioid use or taking any drug known to produce sedation or alter MAC were excluded from the study.

Patients were randomly allocated to predetermined target fentanyl Cp between 2–8 ng/ml. The pharmacokinetic parameters of fentanyl used in CACI were those published by McClain and Hug.⁸ The accuracy of these pharmacokinetics with CACI in a homogeneous surgical population has been established to have a median population performance error of –4% and a precision (10th–90th percentile of the median performance error) of –31–36%.⁹ Each patient was brought to the operating room suite unpremedicated. An intravenous catheter for drug administration was placed in one arm, while a 20-G catheter for blood sampling (*i.e.*, fentanyl and norepinephrine) was inserted into the contralateral radial artery.

Arterial blood pressure, heart rate, peripheral oxygen hemoglobin saturation, end tidal carbon dioxide, and nasopharyngeal temperature were continuously re-

corded and displayed. End tidal carbon dioxide was maintained between 35 and 40 mmHg, and temperature was maintained above 36° C.

All patients were administered 65 µg/kg of d-tubocurarine. They then breathed 70% N₂O in oxygen *via* a tight-fitting face mask for at least 4 min, after which fentanyl was administered *via* CACI (target concentration 10–20 ng/ml) until loss of response to verbal command and loss of the eyelash reflex. With loss of consciousness, 1.5 mg/kg succinylcholine was given to facilitate tracheal intubation, and during laryngoscopy, the trachea was sprayed with 4% topical lidocaine (100 mg) to prevent subsequent movement due to laryngeal stimulation. Immediately following loss of consciousness, the randomized target Cp of fentanyl was entered into CACI. Once the selected concentration was estimated to have been reached, it was held constant until surgical incision.

Arterial blood samples were drawn when a steady fentanyl Cp was assumed to have been obtained preincision and 1 min postincision, to determine fentanyl and norepinephrine Cp. Fentanyl blood samples were collected into heparinized glass tubes and immediately placed on ice. Soon thereafter (within 60 min), the samples were centrifuged and the plasma was frozen at –70° C until they were analyzed. The fentanyl concentration was determined[#] using a previously described RIA technique.¹⁰ The assay was linear over the concentrations measured with a lower limit of detection of 0.2 ng/ml and a coefficient of variation of less than 10%. Samples for norepinephrine concentrations were placed in tubes containing EGTA/glutathione and then centrifuged, and the plasma was stored at –70° C until analyzed.** Norepinephrine was measured using on-line high pressure-performance liquid chromatography with electrochemical detection as previously described.¹¹ The assay was linear over the concentrations measured with a lower limit of detection of 10 pg/ml. The intra- and interassay coefficients of variation were less than 10%.

During skin incision, each patient was monitored for any somatic, autonomic, or adrenergic response. A somatic response was considered as any purposeful bodily movement. All patients were monitored for a somatic response for 1 min after incision. A hemodynamic response was defined as a 15% increase in heart rate or mean blood pressure greater than baseline. Baseline was defined as the mean of three readings taken the day prior to surgery, the morning of surgery, and just prior to induction. An autonomic response was any sign

The fentanyl concentration was determined by Dr. S. Bai, North Carolina State University, Raleigh, North Carolina.

** The plasma was analyzed by Dr. M. Su, Duke University Medical Center, Durham, North Carolina.

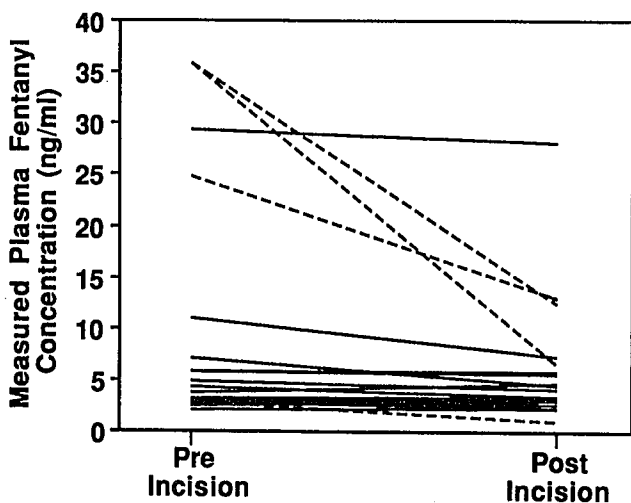


Fig. 1. Pre- and postincision fentanyl concentrations for all patients ($n = 22$). Solid lines represent the patients ($n = 18$) in whom the pre- and postincision fentanyl plasma concentrations were within $\pm 30\%$ of each other. Dashed lines represent the patients in whom the pre- and postincision plasma fentanyl concentrations exceeded $\pm 30\%$ and were not included in the calculation of the Cp50.

of increased autonomic activity such as tearing or diaphoresis, or a 50% increase in norepinephrine concentration above baseline. To ensure a steady concentration was maintained and equilibration between plasma and effect site had occurred, only data from patients in whom the fentanyl Cp at pre- and postincision were within $\pm 30\%$ of each other were included in the statistical analysis.

Utilizing the fentanyl concentration pre-incision, the Cp50 and Cp50-BAR for fentanyl were determined using SAS/STAT Software^{††} from the equation

$$P = 1/1 + e^{-(ax+b)},$$

where P = probability of no response, x is the drug concentration, and a and b are parameters to be determined. Cp50 is then given by $-b/a$.¹² The 67% fiducial limits calculated from ± 1 SD confidence limits on the predicted curve were obtained similarly from the SAS program.

Results

Twenty-two patients were studied. In 18 patients, the fentanyl concentration was maintained within $\pm 30\%$

from pre- to postincision (fig. 1). These 18 patients were used in the determination of Cp50 and Cp50-BAR. Of these 18 patients, 9 were men and 9 were women. Their average age was 33 yr (\pm SD 8, range 22–47) with a weight of 76 kg (\pm SD 17, range 46–96). The average time between the pre- and postincision fentanyl sample was 7 min 31 s (\pm SD 3 min 14 s).

Seven patients moved in response to skin incision (fig. 2). Two patients who moved had a hemodynamic response (one heart rate, one mean blood pressure). No patient who did not move had a 15% or greater increase in blood pressure or heart rate. Two patients who did not move had a greater than 50% increase in norepinephrine concentration. Thus, nine patients had a somatic, hemodynamic, or autonomic response (fig. 3).

For a somatic response, the Cp50 of fentanyl in the presence of 70% N₂O was determined to be 3.26 ng/ml (67% fiducial limits, 2.4 to 4.1 ng/ml) and the Cp50-BAR was 4.17 ng/ml (67% fiducial limits, 3.2 to 5.9 ng/ml). The derived value for the parameter a

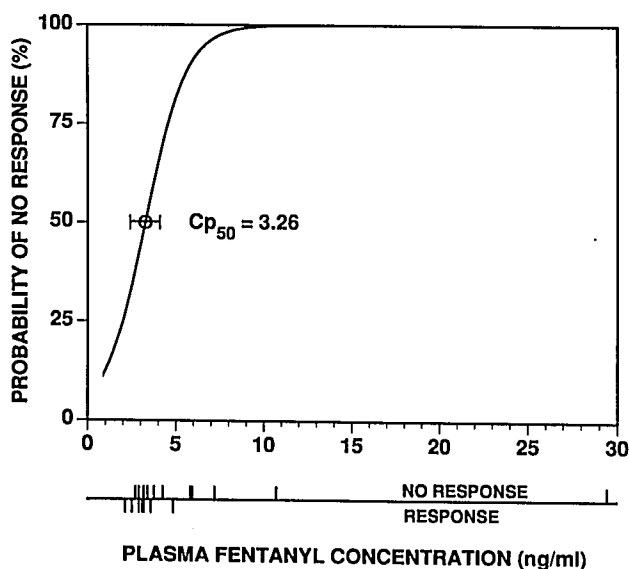


Fig. 2. The tick-mark plot shows the response/no response (movement) versus plasma fentanyl concentrations. Each mark indicates the plasma fentanyl concentration and response to surgical incision. From this data, the predicted probability of no response (movement) plasma fentanyl concentration obtained using logistic regression is plotted in the upper graph. The bar indicates ± 1 SD (67% fiducial limits) of the estimate of the plasma fentanyl concentration producing a 50% probability of no movement at skin incision.

^{††} SAS Institute: SAS Technical Report P-200, SAS/STAT Software: Calls and Logistic Procedures, Release 6.04. Cary: SAS Institute, 1990.

FENTANYL Cp50

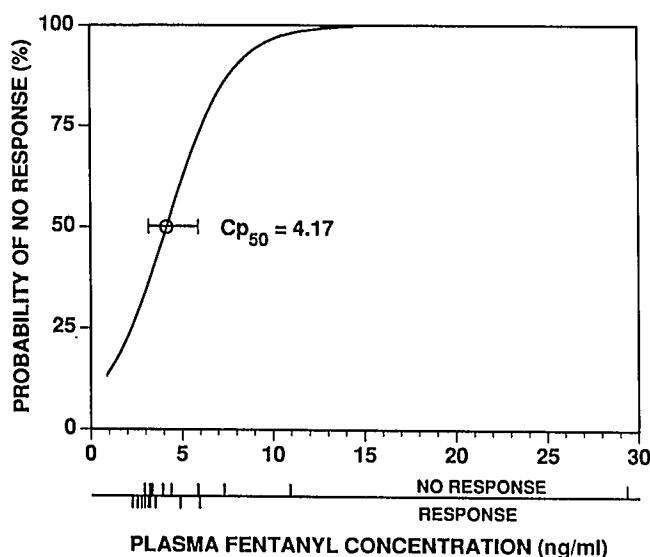


Fig. 3. The tick-mark plot shows the response/no response (movement and hemodynamic or autonomic) versus plasma fentanyl concentrations. Each mark indicates the plasma fentanyl concentration and response to surgical incision. From this data, the predicted probability of no response (movement and hemodynamic or autonomic) versus plasma fentanyl concentration obtained using logistic regression is plotted in the upper graph. The bar indicates ± 1 SD (67% fiducial limits) of the estimate of the plasma fentanyl concentration producing a 50% probability of no response at skin incision.

(which represents the interpatient variability) used in the calculation of the Cp50 was -0.566 , and for the calculation of Cp50-BAR it was -0.858 .

Discussion

We determined the Cp of fentanyl (in the presence of 70% N₂O) required to prevent a somatic response to skin incision, once the plasma and effect site concentrations were in equilibrium, as 3.26 ng/ml. Minimum alveolar concentration has proved extremely useful as a measure of potency, thereby allowing pharmacodynamic comparisons between the potent volatile anesthetics. The Cp50 of the opioids can be considered a MAC equivalent and can provide a similar measure for comparison of opioids.

Minimum alveolar concentration of volatile anesthetics can be determined in the absence of other drugs. Opioids alone cannot provide anesthesia in all patients,¹³ and therefore, when these are used as sole anesthetics, it may be impossible to define a Cp50. Thus,

to determine a measure of anesthetic efficacy of an opioid, it must be combined with another anesthetic. One of two approaches is possible. The first is to determine the ability of the opioid to reduce the MAC of a potent volatile anesthetic.¹⁴ The opioid concentrations producing an equivalent MAC reduction may be considered equipotent. The second approach is to use a predetermined concentration of the second anesthetic (*i.e.*, 70% N₂O) and determine the Cp50 at this (universal) concentration. For this study, we chose this second approach as the Cp50 of alfentanil already had been determined using this method.³ Ausems *et al.* determined the Cp50 (skin incision) of alfentanil as 241 ± 16 ng/ml.³ In their study, the Cp50 was defined both by the incidence of movement and by hemodynamic and autonomic response. Their definition of Cp50 was closer to our definition of Cp50-BAR. To determine Cp50-BAR, we also included the actual measurement of norepinephrine as there may be a poor correlation between observed hemodynamic responses and measured stress hormone changes.¹⁵ Thus, if we compare Ausems alfentanil Cp50 (241 ng/ml) to our fentanyl Cp50-BAR (4.17 ng/ml), fentanyl is 58 times more potent than alfentanil in terms of its anesthetic potency.

Several studies have measured the fentanyl Cp when combined with nitrous oxide during anesthesia. Lehmann *et al.*¹⁶ established the minimum effective venous concentration of fentanyl during anesthesia as 3.17 ± 2.16 ng/ml. A previous study by Glass *et al.*⁹ found that the venous fentanyl Cp required during a nitrous oxide opioid anesthetic was 3–6 ng/ml. Similarly, White *et al.*¹⁷ found venous fentanyl Cp of 1–4 ng/ml were required with nitrous oxide during superficial surgery. These values are in general agreement with the value of the fentanyl Cp50 we obtained in this study.

Another method used to determine the relative potency of opioids has been to determine the concentration required to suppress the spectral edge of the electroencephalogram by 50%.⁴ This concentration for fentanyl was 6.9 ± 1.5 ng/ml and for alfentanil 520 ± 163 ng/ml.⁴ Using this methodology, Scott *et al.* established the potency of fentanyl compared to alfentanil as 1:75.⁴ Although the relationship between suppression of the spectral edge and anesthetic/analgesic potency is not clearly established, this value is in close agreement with our findings.

As mentioned above, an alternative method to establish the anesthetic potency of an opioid is to determine

the concentration providing an equivalent MAC reduction. The MAC reduction of isoflurane by both fentanyl¹⁵ and alfentanil¹⁸ was determined recently. A 50% MAC reduction is produced by 1 ng/ml fentanyl¹⁵ and 38 ng/ml alfentanil.¹⁸ Using this methodology, fentanyl is 40 times more potent than alfentanil. This value is again in close agreement with our determination of the potency of fentanyl relative to alfentanil.

A relative potency between fentanyl and alfentanil of 1:60 differs markedly from the potency ratio of 1:3–10 quoted in previous studies following bolus doses of these drugs.^{19,20} This difference is readily explained both by their different pharmacokinetics and by the differences in onset of effect resulting from the administration of these drugs.⁴ The onset of effect following a bolus dose depends on both the $t_{1/2k_{co}}$ (*i.e.*, the half time for equilibration between the plasma and effect compartment) and the distribution pharmacokinetics of the drug. The $t_{1/2k_{co}}$ (as determined by suppression of the spectral edge) is 6.4 ± 1.3 min for fentanyl and 1.1 ± 0.3 min for alfentanil.⁴ Because of these markedly different values, both the time course of effect and the peak effect from an equipotent dose will be markedly different for these two drugs. The time to peak effect following a bolus dose of alfentanil is predicted as 82 s, compared to 231 s for fentanyl.²¹ Thus, comparison following a single bolus dose is an unreliable method of determining relative potency.

The concentration of opioid at the effect site determines drug effect. Because of hysteresis, it is important to maintain a steady C_p for 3–4 $t_{1/2k_{co}}$ for equilibration to occur between C_p and effect site concentration. In attempting to determine the C_p50 of fentanyl, this would require 15–20 min. To enable us to induce an anesthetic state without prolonging the anesthetic induction time, we initially used very high C_p . This also enabled us to achieve the effect concentration more rapidly than waiting 20 min (cf overpressure with volatile anesthetics). By doing this, it is possible that the effect site concentration may have exceeded the target C_p to which the patient was randomized. To minimize this possibility, the initial high C_p was maintained for as short a period as possible, and once the allocated C_p had been obtained, it was maintained until skin incision to allow for equilibration between the C_p and the effect site concentration to occur. Using computer simulations in each individual patient and based on a fentanyl $t_{1/2k_{co}}$ value of 6.4 min, the median theoretical

effect compartment concentration was 7.5% (range 0.5–26.3%) higher than the theoretical target concentration at incision. This would imply that the C_p50 values measured at true equilibrium between plasma and the biophase would be slightly higher (7.5%) than we determined. This difference is small compared to the interpatient variability of the C_p50 .

In conclusion, using CACI (a pharmacokinetic model driven infusion device), we determined the concentration of fentanyl required to prevent a somatic response (C_p50) and an autonomic response (C_p50 -BAR) to skin incision in the presence of 70% N_2O . The C_p50 was 3.26 ng/ml, and the C_p50 -BAR was 4.17 ng/ml. This implies that, when considering C_p , fentanyl is approximately 60 times more potent than alfentanil in its anesthetic effect.

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