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Isoflurane Minimum Alveolar Concentration Reduction by Fentanyl

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Background: Isoflurane is commonly combined with fentanyl during anesthesia. Because of hysteresis between plasma and effect site, bolus administration of fentanyl does not accurately describe the interaction between these drugs. The purpose of this study was to determine the MAC reduction of isoflurane by fentanyl when both drugs had reached steady biophase concentrations.

Methods: Seventy-seven patients were randomly allocated to receive either no fentanyl or fentanyl at several predetermined plasma concentrations. Fentanyl was administered using a computer-assisted continuous infusion device. Patients were also randomly allocated to receive a predetermined steady state end-tidal concentration of isoflurane. Blood samples for fentanyl concentration were taken at 10 min after initiation of the infusion and before and immediately after skin incision. A minimum of 20 min was allowed between the start of the fentanyl infusion and skin incision. The reduction in the MAC of isoflurane by the measured fentanyl concentration was calculated using a maximum likelihood solution to a logistic regression model.

Results: There was an initial steep reduction in the MAC of isoflurane by fentanyl, with 3 ng/ml resulting in a 63% MAC reduction. A ceiling effect was observed with 10 ng/ml providing only a further 19% reduction in MAC. A 50% decrease in MAC was produced by a fentanyl concentration of 1.67 ng/ml.

Conclusions: Defining the MAC reduction of isoflurane by all the opioids allows their more rational administration with inhalational anesthetics and provides a comparison of their relative anesthetic potencies. (Key words: Analgesics, opioid: fentanyl. Anesthetics, volatile: isoflurane; minimum alveolar concentration. Potency: minimum alveolar concentration.)

THE minimum alveolar concentration (MAC) of volatile anesthetic drugs has been used as a measure of anesthetic potency.¹ At present, no anesthetic drug is commonly used alone to provide all the necessary com-

ponents of general anesthesia. Therefore, it is important to define the properties of the interaction between the different anesthetic drugs that may be used in combination. It is generally accepted that, when combining potent volatile anesthetics, their MACs are simply additive.^{1,2} However, the effect of combining intravenous anesthetics or opioids with potent volatile drugs has been less clearly established. All studies in humans attempting to quantify the MAC reduction of potent volatile anesthetics by the opioids have utilized a bolus dose technique for administering the opioid.³⁻⁵ In a previous study, in which a bolus dose of fentanyl was administered and its plasma concentration measured at skin incision, a profound interaction was noted.⁵ When defining these drug interactions, it is critical that both drugs have reached a steady biophase (effect compartment) concentration.^{6,7} After a bolus dose, the plasma concentration is continuously decreasing and there is an inconsistent relationship (hysteresis) of the plasma concentration to effect.^{6,7} Thus, the interaction previously observed between fentanyl and the potent volatile anesthetic did not accurately determine this interaction.⁵

This study was designed to more accurately determine the MAC reduction of isoflurane by fentanyl by ensuring that both drugs had reached steady biophase concentrations.

Materials and Methods

Approval was obtained from the Duke Institutional Review Board for the project and all patients signed a written informed consent. Unpremedicated, ASA physical status 1 or 2 patients of both sexes, between the ages of 20 and 60 yr, scheduled for elective surgery, were included in the study. The following patients were excluded from the study: 1) those in whom an inhalational induction was contraindicated, 2) those having any significant cardiovascular, respiratory, hepatic or renal disease, 3) those receiving medications known to affect MAC, or having a history of either alcohol or drug abuse, and 4) those in whom any sudden move-

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ment may have been dangerous, *e.g.*, those having surgery on the head or neck or those placed in the prone position.

Patients were initially randomly allocated into one of four different groups (fig. 1). Group one received no fentanyl, while groups two, three, and four each received predicted target plasma concentrations of 0.8, 1.5, and 3.0 ng/ml. An additional group of eight patients was added at the conclusion of the study to more clearly define the MAC reduction at fentanyl concentrations greater than 3 ng/ml. Fentanyl was administered using a pharmacokinetic model-driven infusion device known as CACI (Computer Assisted Continuous Infusion) that is capable of delivering fentanyl to a desired constant plasma concentration.⁸ The pharmacokinetic set used for fentanyl in CACI were those published by McLain and Hug.⁹ This pharmacokinetic set has previously been tested in a homogeneous group of surgical patients, in which it provided a nonsignificant bias and a precision (10th to 90th percentile of the median performance error) of -31% to 26%.⁵

Patients in each group were also randomly allocated to receive predetermined end-tidal isoflurane concentrations (fig. 1). These concentrations were chosen to provide a range that would provide both adequate and inadequate anesthesia at each fentanyl concentration, and were based on data from a previous MAC reduction study.⁵ A Puritan Bennett Anesthetic Agent Monitor 222[®] (Wilmington, MA) was used to measure end-tidal isoflurane concentrations. Before use with each patient, a two-point calibration of the agent monitor using a standard calibration gas was performed after allowing a warm-up period of 30 min. The fentanyl and isoflurane concentrations used for induction of

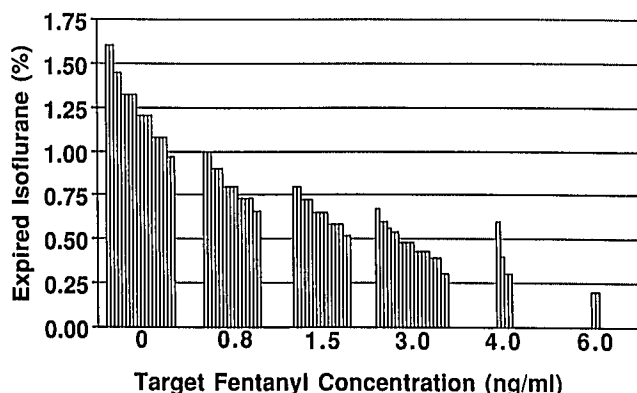


Fig. 1. Randomization scheme. End-tidal isoflurane concentrations for each subject in each of the predicted fentanyl groups.

anesthesia in this study were based on those used in a previous MAC-reduction study.⁵

Before induction of anesthesia, the target plasma concentration of fentanyl (according to the randomization schedule) was entered into CACI. The fentanyl infusion and gaseous induction with increasing concentrations of isoflurane in oxygen were started simultaneously. After loss of consciousness, succinylcholine (1 mg/kg intravenously) was given. This was followed by laryngoscopy and tracheal intubation. Before skin incision, the return of neuromuscular function was checked using a peripheral nerve stimulator. Immediately after tracheal intubation, the inspired end-tidal concentration was adjusted to maintain the measured end-tidal concentration constant at the value preselected according to the randomization schedule. Patients' lungs were mechanically ventilated to normocapnia and body temperature was maintained above 35.5° C during the period of the study. Blood samples for plasma fentanyl levels were taken from an indwelling intravenous catheter in the arm contralateral to that in which the fentanyl infusion was occurring. These samples were taken at 10 min after the start of the infusion and 5 min before and immediately after incision to ensure that plasma fentanyl levels remained constant during the study. A minimum period of 20 min after the start of the fentanyl infusion was allowed before skin incision to allow steady state conditions to develop between the plasma and brain effect compartment.^{7,10} The fentanyl samples were immediately placed in heparinized vacutainers on ice. As soon as possible thereafter (within 60 min), the samples were centrifuged and the plasma separated and stored at -70° C for subsequent analysis. The plasma concentration of fentanyl was measured by radioimmunoassay, using fentanyl antisera and tritiated fentanyl (Fentanyl Radioimmunoassay kit, Janssen Life Sciences, Piscataway, NJ).^{11,12} The lower limit of detection of the assay was 0.2 ng/ml. The assay was linear over the concentration range measured and the coefficient of variation was less than 10%. The desired end-tidal concentration was held constant for at least 15 min before skin incision to allow adequate time for alveolar and brain isoflurane partial pressures to equilibrate.¹

Patients were observed for movement for 60 s after incision, with movement defined as gross purposeful movement in response to incision. Coughing, chewing, or swallowing was not considered to be movement.¹³ The MAC for isoflurane at the measured fentanyl plasma concentrations obtained just before skin incision was

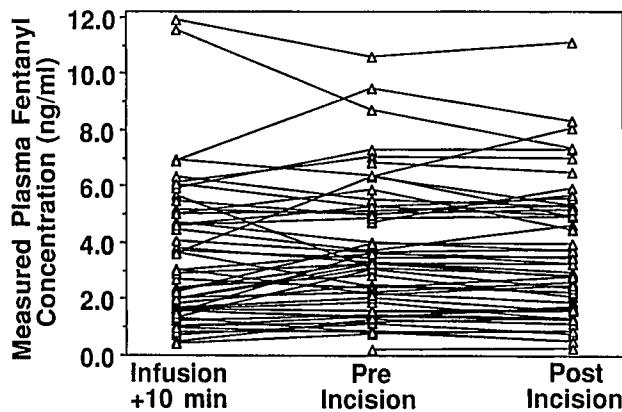


Fig. 2. Measured plasma fentanyl concentrations (ng/ml) plotted at 10 min pre- and postincision.

calculated using a maximum likelihood solution to a logistic regression model⁵ (see Appendix). To insure that fentanyl concentrations were stable at the time of skin incision, only patients in whom the pre- and postincision fentanyl plasma concentrations were within $\pm 30\%$ or within 0.5 ng/ml of each other were included in the analysis.

Results

A total of 77 patients were enrolled in the study. However, four patients were excluded from the subsequent analysis because the measured pre- and postincision plasma concentrations were not within 30% or 0.5 ng/ml of each other. Thus, the results of 73 patients are presented. Of these patients, 30 were men and 43 were women, with an average age of 36 ± 10 yr (range 20–57 yr) and weighing 75 ± 15.0 kg (range 46–123 kg).

The measured plasma fentanyl concentrations tended to be higher than the predicted concentrations. However, the measured fentanyl concentrations in each individual remained relatively constant at 10 min pre- and postincision (fig. 2). The preincision fentanyl concentrations, which were those used in the statistical analyses, ranged from 0 to 10.6 ng/ml.

The MAC reduction of isoflurane by fentanyl is presented in figure 3. In our study population, the MAC of isoflurane, when calculated from the isoflurane-only group, was 1.23% (95% C.I. 0.95, 1.51) (fig. 4). Fentanyl 1 ng/ml resulted in a 39% MAC reduction (table 1). Increasing the fentanyl plasma concentration to 3 ng/ml resulted in a further MAC reduction; specifically, 63%. Fentanyl concentrations greater than 3 ng/ml

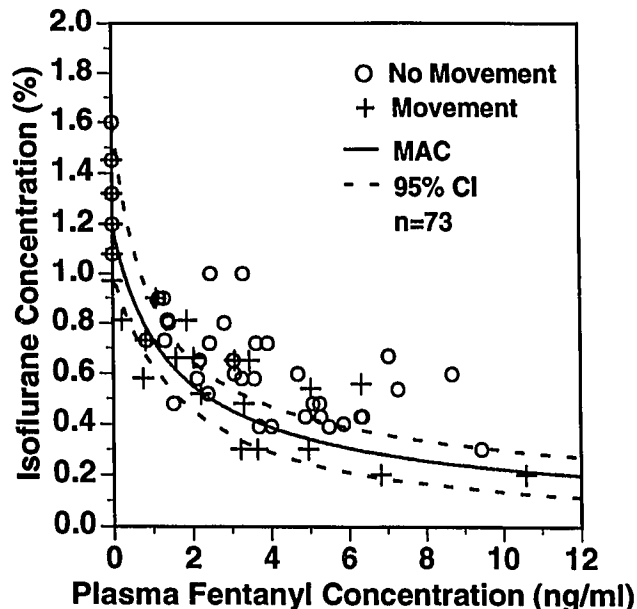


Fig. 3. Maximum likelihood (logistic regression) solution for the MAC reduction of isoflurane by increasing concentrations of fentanyl is represented by the solid line. The 95% confidence intervals of the isoflurane MAC are also plotted as dashed lines.

produced a limited further reduction in MAC. The maximum MAC reduction over the concentration range studied (up to 10.6 ng/ml) was 82%. A 50% MAC reduction of isoflurane was produced by 1.67 (95% fiducial limits 1.11, 2.38) ng/ml fentanyl.

Discussion

The aim of our study was to determine the reduction of the MAC of isoflurane by different steady plasma concentrations of fentanyl, once equilibration had occurred between the plasma fentanyl concentration and its theoretical effect compartment.⁷ This has not previously been done in humans.

There have been many studies to determine the extent to which opioids reduce the MAC of volatile anesthetic agents, but the majority of these studies have been done in animals.^{14–19} A small number of studies have been performed in humans, but these did not attempt to produce steady plasma opioid concentrations.^{3–5} When attempting to define drug interactions, it is important to

§ Murphy MR, Hug CC: Efficacy of fentanyl in reducing isoflurane MAC; Antagonism by naloxone and nalbuphine (abstract). *ANESTHESIOLOGY* 59:A338, 1983

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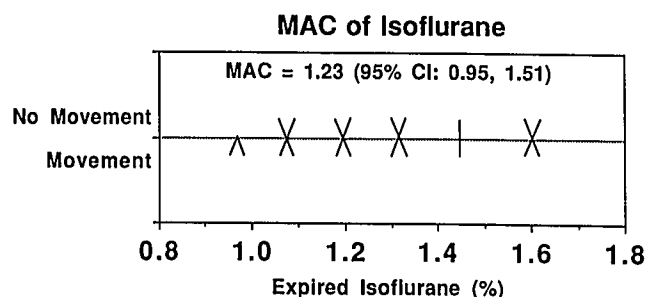


Fig. 4. The isoflurane concentrations at which patients did or did not move when only isoflurane was administered. The concentration is plotted along the x axis; an upward tick represents a patient that did not move, and a downward tick a patient that did move.

ensure that all drugs under investigation have reached steady concentration conditions, in both the plasma and the theoretical effect compartment.^{6,7,9,15} Fentanyl, when given intravenously, exhibits hysteresis whereby the physiologic effect, as measured by the EEG, lags behind the plasma concentration. The half life for transfer to the theoretical effect compartment ($T_{1/2}$ KeO) is 6.4 ± 1.3 min.⁷ In our study, we allowed a minimum of three KeO half lives (approximately 20 min) to elapse between initiating the fentanyl infusion and skin incision (*i.e.*, 95% of equilibration between the plasma and effect site had occurred). The fentanyl was administered *via* CACI so that the desired plasma concentration was obtained rapidly. This ensured that steady state conditions were achieved for fentanyl between the plasma and the theoretical effect compartment at the time of skin incision. Venous samples were obtained as we have previously demonstrated, such that, after 10 min of fentanyl administration by CACI, arterial and venous fentanyl concentration differences are minimal.⁸ The end-tidal isoflurane concentration was held constant at the desired concentration for a minimum of 15 min to allow the alveolar and brain partial pressure to equilibrate.¹³ Thus, at the time of skin incision, the measured fentanyl plasma concentration and the measured end-tidal isoflurane concentration were a true reflection of the effect compartment concentration. Before the initiation of this study, we chose to exclude those patients in whom the pre- and postincision fentanyl samples were not within either 0.5 ng/ml or $\pm 30\%$ of each other, to insure a steady biophase concentration. Ideally, the pre- and postincision fentanyl concentrations should be identical. As we were dependent on CACI to maintain this steady concentration, such precision would be impossible.

Our previous data with CACI administration of fentanyl demonstrated that concentrations could be maintained within $\pm 30\%$ in the majority of patients; therefore, this was chosen as the degree of variability that we would accept during this study.⁸

The MAC of isoflurane obtained in this study was 1.23%. This is very similar to the previously determined isoflurane MAC in humans, although the study methodology and statistical analysis used in this study were different than the classic Dixon up-down method.^{1,13} The interaction of isoflurane along a continuum of fentanyl concentrations is more accurately calculated using logistic regression analysis. When using logistic regression analysis, it is necessary to randomize to predetermined groups, rather than randomizing patients during the study according to the outcome of the previous patient. From this study, we have demonstrated that fentanyl produces an initial steep decrease in the MAC of isoflurane. This decrease then reaches a plateau with minimal further reduction in MAC at a fentanyl concentration greater than 3 ng/ml of fentanyl. At 3 ng/ml, the MAC of isoflurane is reduced by 63%. Doubling the plasma concentration from 3 to 6 ng/ml only produces a further 12% reduction in MAC, with a maximum MAC reduction of just greater than 80% being achieved at plasma fentanyl concentrations of 10 ng/ml. This rapid flattening of the curve in the plot of plasma fentanyl concentration *versus* MAC of isoflurane (fig. 3) suggests that a ceiling effect exists in the interaction of fentanyl on the MAC reduction of isoflurane.

In the first MAC-reduction studies, in which both drugs were administered to reach steady biophase concentrations, Murphy *et al.*¹⁵ § showed that fentanyl given by continuous infusion to dogs at a plasma concentration of 6 ng/ml produced a 63% reduction in the MAC of isoflurane. A fentanyl concentration of 21

Table 1. MAC and MAC Reduction of Isoflurane by Increasing Concentrations of Fentanyl

| Fentanyl Concentration (ng/ml) | MAC of Isoflurane (95% CI, %) | Isoflurane MAC Reduction (%) |
|--------------------------------|-------------------------------|------------------------------|
| 0 | 1.20 (0.99, 1.62) | — |
| 1 | 0.73 (0.63, 0.88) | 39 |
| 2 | 0.55 (0.45, 0.65) | 54 |
| 3 | 0.45 (0.35, 0.54) | 63 |
| 6 | 0.30 (0.21, 0.38) | 75 |
| 10 | 0.22 (0.13, 0.30) | 82 |

MAC = minimum alveolar concentration; CI = confidence interval.

ng/ml produced very little (67%) further reduction in the MAC of isoflurane.¹⁵ § These results are in agreement with the ceiling effect seen in our study. Sufentanil,¹⁷ alfentanil,¹⁴ and morphine,¹⁶ given to animals, resulted in a similar ceiling in the maximal MAC reduction of the potent volatile anesthetic. In humans, the MAC reduction of the potent volatile anesthetics has only been studied after a single dose of the opioid. Morphine, 10–12 mg, given subcutaneously produced a 20% reduction in the MAC of fluroxine.³ Morphine premedication, 8–15 mg, resulted in a 7% decrease in the MAC of halothane.⁴ These small reductions in MAC produced by morphine are in contrast to the 48% and 63% reduction in desflurane MAC after 3 and 6 µg/kg fentanyl, respectively.⁵ The degree of MAC reduction of the potent volatile anesthetic obtained after a bolus dose of the opioid cannot be compared to the MAC reduction observed in our study, because the resultant opioid concentration after a bolus dose is markedly dependent on the timing between administration of the opioid and application of the stimulus to evaluate MAC. This is because of the continuously changing concentration and hysteresis observed after the administration of a bolus dose of the opioid.

There are important clinical implications of the initial steep reduction in MAC of isoflurane by fentanyl followed by a ceiling effect beyond 3 ng/ml fentanyl. Substantial reduction in isoflurane requirement (40–60%) can be achieved at low (1–3 ng/ml) plasma concentrations of fentanyl. Fentanyl given as an initial bolus dose of 3 µg/kg over 5 min, followed by an infusion of 1 µg·kg⁻¹·h⁻¹, will achieve a 1-ng/ml fentanyl plasma concentration. Doubling these dosages will result in doubling the fentanyl plasma concentration. There is also little to be gained in terms of MAC reduction of isoflurane by increasing plasma fentanyl to greater than 2–3 ng/ml, because fentanyl plasma concentrations greater than 2 ng/ml may be associated with significant respiratory depression.⁹ These values may not necessarily apply uniformly to the interaction of fentanyl with other potent volatile anesthetics. Studies in dogs have shown that an equal reduction of MAC by fentanyl requires higher fentanyl plasma concentrations for enflurane than isoflurane.^{15,16} This may be because enflurane may have some cerebral excitatory effects. Further studies in humans are needed to ascertain

whether patients anesthetized with enflurane require a higher concentration of fentanyl to produce the same degree of MAC reduction as seen with isoflurane.

Establishing the relative anesthetic potencies of the different opioids is difficult. Comparing opioids after a single bolus dose does not account for the lag time required for the drug to enter the theoretical effect compartment.^{6,7,10} It is also important that a precise measure of efficacy is chosen when establishing the potency of an opioid. Determining the effect of different opioids on postoperative pain is another method employed; however, it lacks an objective endpoint. Attempts have also been made to establish relative opioid potency by determining the dose requirements during a nitrous oxide-opioid anesthetic.²⁰ Although this study was well designed, it also lacked a single well defined endpoint. Depression of the EEG has been used as a measure of effect to determine the relative potency of fentanyl to alfentanil.⁷ However, the relationship of EEG depression to anesthetic potency of the opioids is not clearly established.

Movement at skin incision is the standard measure for assessment of anesthetic effect.¹ Thus, the concept of Cp50 (skin incision) has been proposed for determining the potency of intravenous anesthetics.²¹ The Cp50 (skin incision) for an opioid is defined as the plasma concentration, in the presence of 66% nitrous oxide, that will prevent a somatic, hemodynamic, or somatic response to skin incision. The Cp50 for alfentanil, fentanyl, and sufentanil have been determined and provide, like MAC, a measure of potency.^{21,22} ¶ The ability of an opioid (at a steady concentration and when equilibrated with the effect compartment) to reduce the MAC of a potent volatile anesthetic provides a similar objective measure of its analgesic potency. Thus, opioid concentrations producing the same MAC reduction may be considered equipotent. In this study, we have defined the plasma concentration of fentanyl that produces a 50% MAC reduction of isoflurane. This value can then be compared to that of other opioids that produce the same MAC reduction, and their relative potency can be established.

In conclusion, we determined the MAC reduction of isoflurane by fentanyl by using a pharmacokinetic model-driven infusion device to provide constant plasma fentanyl concentrations. The reduction of the MAC of isoflurane by fentanyl was greatest with plasma fentanyl concentrations of up to 3 ng/ml (63% MAC reduction). At higher plasma fentanyl concentrations

¶ Doherty MA, Glass PSA, Jacobs JR, Reves JG: CP50 for fentanyl (abstract). ANESTHESIOLOGY 71:A231, 1989

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(3–10 ng/ml), there was little further reduction in the MAC of isoflurane.

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Appendix

If P is the probability of a response, the odds of a response is $P/(1 - P)$. To determine which factors (concentrations of the two drugs) influence the probability of response, the logistic model (where the log-odds is expressed as a linear function of the explanatory factors) can be used:

$$\ln(P/1-P) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{1,2} x_1 x_2,$$

where P = probability of response, x_1 is the concentration of drug 1, x_2 is the concentration of drug 2, β_0 is the intercept, β_1 is the slope coefficient for drug 1, β_2 is the slope coefficient for drug 2, and $\beta_{1,2}$ is the measure of the interaction of the two drugs acting jointly. If the C_p represents the minimum drug concentration at which $P\%$ of the patients will be effected, to solve for $P = 0.5$ (50% level):

$$C_{50}(x_1 \langle sv \rangle x_2) = -(\beta_0 + \beta_2 x_2) / (\beta_1 + \beta_{1,2} x_2).$$

For this study, we used $x_1 = \ln(1 + \text{concentration})$ of drug 1 (isoflurane), and $x_2 = \ln(1 + \text{concentration})$ of drug 2 (fentanyl), where \ln is natural logarithm function. The addition of 1 to the concentration permits the taking of the logarithm of the dose without altering the shape of the response curve. Parameter estimates were $\beta_0 = 0.6673$, $\beta_1 = -3.6952$, $\beta_2 = -2.5982$, and $\beta_{1,2} = 0$.