The Interaction of Fentanyl on the Cp₅₀ of Propofol for Loss of Consciousness and Skin Incision

Peter S. A. Glass, M.B., Ch.B.¶

Background: We have previously demonstrated that the minimum alveolar concentration of isoflurane at 1 atm that is required to prevent movement in 50% of patients or animals exposed to a maximal noxious stimulus is markedly reduced by increasing fentanyl concentrations. Total intravenous anesthesia with propofol is increasing in popularity, yet the propofol concentrations required for total intravenous anesthesia or the interaction between propofol and fentanyl have not yet been defined.

Methods: Propofol and fentanyl were administered is a computer-assisted continuous infusion to provide pseudo-steady-state concentrations and allow equilibration between plasma-blood concentration and their biophase concentration. For the induction of anesthesia patients were randomly allocated to receive propofol only or propofol plus fentanyl 0.2, 0.8, 1.5, 3.0, and 4.5 ng/mL. In each group patients were randomized to target propofol concentrations of 1.5–10 μg/mL. At 7 and 10 min arterial blood samples were taken for subsequent measurement of propofol and fentanyl concentrations. At 10 min loss of consciousness was assessed by the patients' ability to respond to a simple verbal command. Thereafter a new target concentration of propofol was entered to ensure loss of consciousness, and succinylcholine was administered to facilitate tracheal intubation. Patients were repositioned to a new target concentration of propofol (1–19 μg/mL) until skin incision. Before skin incision and 1 min after skin incision, arterial blood samples were again obtained for subsequent measurement of fentanyl and propofol concentrations. At skin incision and for 1 min the patient was observed for purposeful movement. Only samples in which the pre- and poststimulus drug concentrations were within 35% of each other were included. The propofol blood concentration at which 50% or 95% of patients did not respond to verbal command (Cₚ₅₀ and Cₚ₉₅, respectively) and to skin incision (Cₚ₉₀ and Cₚ₉₁, respectively), were calculated by logistic regression.

Results: There were 56 evaluable patients for calculating the propofol Cₚ₅₀ and 53 patients for calculating the propofol Cₚ₉₀. For propofol alone the Cₚ₅₀ was 3.3 μg/mL and the Cₚ₉₀ was 5.4 μg/mL. Increasing fentanyl concentrations reduced the Cₚ₅₀ (P = 0.03), and increasing age decreased the Cₚ₅₀ (P = 0.04). For propofol alone the Cₚ₉₀ was 15.2 (95% confidence interval 7.6–22.8) μg/mL and the Cₚ₉₀ was 27.4 μg/mL. Increasing fentanyl concentrations markedly reduced the Cₚ₉₀ (P < 0.01), with a 50% reduction in Cₚ₉₀ produced by 0.63 ng/mL fentanyl. The propofol Cₚ₉₀ was decreased by 63% with 1 ng/mL fentanyl and 89% by 3 ng/mL fentanyl. At higher fentanyl concentrations the decrease in Cₚ₉₀ was proportionally less, demonstrating a ceiling effect.

Conclusions: We defined the propofol concentration required for loss of consciousness and showed that it is reduced by increasing fentanyl concentration and by increasing age. The propofol concentration (alone) adequate for skin incision is high but is markedly reduced by fentanyl. A ceiling effect in the Cₚ₉₀ for propofol is seen with fentanyl concentrations greater than 3 ng/mL. (Key words: Anesthetics, intravenous; fentanyl; propofol. Equipment: computers. Potency anesthetic.)

PROPFOOL is an intravenous anesthetic initially introduced for the induction of anesthesia. It has recently been approved in the United States for the maintenance of anesthesia either combined with nitrous oxide or a potent opioid for total intravenous anesthesia. It is important to establish the therapeutic concentrations of propofol for loss of consciousness and surgery if it is to be used for the maintenance of anesthesia. For the potent volatile anesthetics the minimum alveolar concentration of anesthetic at 1 atm that is required to prevent movement in 50% of patients or animals exposed to a maximal noxious stimulus (MAC) provides a measure of potency and as a result a guide to the

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 26A.
therapeutic concentrations necessary for anesthesia. For intravenous anesthetics, the index of potency has been defined in terms of the plasma concentration required to prevent a response in 50% of patients (Cp50) to surgical stimulus and similarly is a measure of potency and a guide for therapeutic concentrations.\textsuperscript{2,3}

There are a number of studies that provide values for whole-blood propofol concentrations required for anesthesia, but these studies have been done in the presence of other drugs that are likely to alter the Cp50 of propofol, or when the biophase (effect compartment) has not yet reached equilibrium with the measured blood concentration. Pharmacokinetic model-driven infusion devices such as those designed for computer-assisted continuous infusion (CACI) can now be used to deliver and maintain constant target concentrations of propofol, thus providing a measured blood concentration that has equilibrated with the effect compartment.\textsuperscript{4}

Only after the anesthetic potency of propofol has been defined can its interaction with other intravenous anesthetic drugs be quantified. Opioids reduce the requirements of other anesthetic drugs for surgery. The effect of increasing plasma concentrations of fentanyl on reducing the MAC of isoflurane is significant.\textsuperscript{5} As the interest in total intravenous anesthesia with propofol increases it is important to clearly characterize its interaction with opioids both for loss of consciousness and surgery.

This study was designed to determine (1) the whole-blood propofol concentration at which 50% of patients do not respond to a simple verbal command (Cp50s), (2) the whole-blood propofol concentration at which 50% of patients do not move purposefully at skin incision (Cp50i), and (3) the reduction of Cp50s and Cp50i by fentanyl, when both drugs have reached steady biophase concentrations.

**Materials and Methods**

Approval for this study was obtained from the Duke Institutional Review Board for human investigation. All patients signed a written informed consent. Nonpremedicated, ASA physical status 1 or 2 male and female patients, aged 20–55 yr, scheduled for elective surgery were included in the study. Patients were excluded if (1) there was a history of esophageal reflux, hiatal hernia, significant obesity or peptic ulcer disease; (2) patients had any significant cardiovascular, respiratory, hepatic, or renal disease; (3) patients receiving any medications known to affect anesthetic requirements of propofol or who had a history of alcohol or drug abuse; (4) sudden movement at skin incision may have been dangerous e.g. patients undergoing surgery in the prone position or receiving head and neck surgery; (5) patients were hard of hearing.

Patients were brought to the operating room nonpremedicated. Before induction of anesthesia a venous catheter was inserted for drug administration and a catheter inserted into the radial artery for blood sampling.

**Measurement of Concentrations for Prevention of Response to Verbal Command**

For induction of anesthesia patients were randomly allocated into one of six different groups. Group 1 received propofol only, while groups 2–6 received propofol and fentanyl (fig. 1). Both propofol and fentanyl were administered using a pharmacokinetic model-driven CACI device. The CACI device is capable of administering intravenous drugs to constant target plasma concentrations. The pharmacokinetic parameters used in CACI for fentanyl and propofol are listed in table 1. Groups 1–6 received fentanyl to target plasma concentrations of 0, 0.2, 0.8, 1.5, 3.0, and 4.5 ng/ml respectively. Within each group, patients were randomized to receive predetermined target concentrations of propofol ranging from 1.5 to 10 µg/ml (fig. 1). These values were selected on the basis of our previous experience with propofol and fentanyl for total intravenous anesthesia and other MAC reduction studies.\textsuperscript{5}

Before induction, the randomized target concentrations of propofol and fentanyl were entered into the

![Randomization Scheme for Loss of Consciousness (Cp50s)](image-url)

Fig. 1. Target concentrations of propofol and fentanyl to which patients were randomized for assessment of loss of response to verbal command (Cp50s).

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Table 1. Pharmacokinetic Values Used in CACI for the Administration of Propofol and Fentanyl

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Propofol (min)</th>
<th>Fentanyl (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_d$ (L/kg)</td>
<td>0.0767</td>
<td>0.3560</td>
</tr>
<tr>
<td>$k_{10}$ (min)</td>
<td>0.0035</td>
<td>0.0410</td>
</tr>
<tr>
<td>$k_{20}$ (min)</td>
<td>0.2046</td>
<td>0.1850</td>
</tr>
<tr>
<td>$k_{30}$ (min)</td>
<td>0.0066</td>
<td>0.1030</td>
</tr>
<tr>
<td>$k_{40}$ (min)</td>
<td>0.2730</td>
<td>0.1410</td>
</tr>
<tr>
<td>$k_{50}$ (min)</td>
<td>0.0036</td>
<td>0.0200</td>
</tr>
</tbody>
</table>

CACI device. To ensure rapid equilibration between the plasma and effect compartment the fentanyl concentration entered into the CACI device was 1.5 times the randomized target concentration (i.e., 0, 0.3, 1.2, 2.3, 4.5, or 6.75 ng/ml). At 2 min the fentanyl concentration entered into the CACI device was then reduced to the actual target concentrations of 0, 0.2, 0.8, 1.5, 3 or 4.5 ng/ml respectively. The propofol and fentanyl (if being given) were started simultaneously with the patient breathing 100% oxygen. To prevent the discomfort caused by propofol, lidocaine (0.5 mg/kg), was given intravenously before any drug administration.

Blood samples for whole-blood propofol and plasma fentanyl concentrations were taken 7 and 10 min after the start of the infusion(s). These samples were taken to ensure that steady plasma propofol and fentanyl levels were being maintained. These blood samples for fentanyl and propofol were collected in heparinized tubes and placed on ice. The fentanyl samples were centrifuged and the plasma stored at −70°C until their concentrations were measured (by S. Bai, at the North Carolina State School of Veterinary Medicine, Raleigh-Durham, NC) by radioimmunoassay. The propofol samples were refrigerated at −4°C and their concentrations measured (by A.T.C., at Duke University Medical Center) by high-performance liquid chromatography.

If patients became apneic during the 10-min infusion their lungs were gently manually ventilated via face mask to maintain end-tidal carbon dioxide at 35–40 mmHg. Ten minutes after the infusion was initiated patients were assessed as being awake or asleep by having their name firmly called out and being instructed to open their eyes. If patients failed to open their eyes they were deemed asleep.

Measurement of Concentrations for Prevention of Response to Skin Incision

On completion of the above assessment, the target concentration of propofol was either maintained or increased using CACI to a blood concentration sufficient to ensure loss of consciousness. Succinylcholine 1 mg/kg i.v. was administered to facilitate tracheal intubation. The patients lungs were mechanically ventilated with 100% oxygen to normocapnia and normal body temperature was maintained above 35.5°C during the period of the study.

For skin incision patients were randomized to receive a new predetermined target propofol concentration ranging from 1 to 19 μg/ml (fig. 2). The propofol concentration was maintained for at least 10 min before skin incision to ensure equilibration between plasma and the effect compartment. A return of neuromuscular function was confirmed using a peripheral nerve stimulator. Further blood samples for propofol and fentanyl concentrations were taken approximately 3 min before and just after skin incision. The patient was observed for gross purposeful movement for 60 s after incision. Coughing, chewing or swallowing was not considered as movement. If hypotension occurred, at any time, at the randomized target concentrations of propofol and fentanyl, the patient’s blood pressure was restored by a combination of fluid administration and ephedrine as necessary.

The pre- and postassessment samples were compared to insure that a steady concentration was being maintained. Only paired samples (i.e., 7- and 10-min samples or pre- and postincision samples) that had concentrations within ±35% of each other were included in the statistical analysis. From these paired samples the blood concentration at 7 min and after skin incision were the values used in the model. The responders at
Cp50 REDUCTION OF PROPOFOL BY FENTANYL

induction (awake or asleep) and at skin incision (movement or no movement) were modeled using logistic regression with the natural log of the drug concentration as predictor variables. In addition the product of the log of the drug concentrations was included in the model to determine an interaction (deviation from linearity) effect. The Cp50 and the concentration of propofol in blood required to prevent response in 95% of patients (Cp95) were determined from each model by substituting 0.5 (for Cp50) or 0.95 (for Cp95) and solving for the corresponding drug dose. The variance of the Cp50 or Cp95 was calculated from the model estimates, and covariances by statistical differentials. 95% confidence intervals were then calculated from this variance estimate. All other values are reported as means ± SD.

Results

Seventy-nine patients (39 men and 40 women) entered the study. Their average age was 37.7 ± 9.5 yr (range 21–55 yr); their average weight 77.5 ± 17 kg (range 50–123 kg). In 9 patients, for technical reasons, either propofol or fentanyl concentrations could not be assayed; these patients were excluded from all further data analysis. The median performance error of CACI with propofol was –2% and for fentanyl was 93%. The median absolute performance error for propofol was 30% and for fentanyl was 94%.

Concentrations for Prevention of Response to Verbal Command

The measured plasma fentanyl concentrations tended to be higher than the concentrations predicted by CACI, ranging from 0 to 8.65 ng/ml. The propofol whole-blood concentrations ranged from 0.42 to 9.64 µg/ml. The propofol and fentanyl concentrations remained relatively constant for each individual when measured at 7 and 10 min.

In the 70 patients for whom drug concentrations were available, 14 were excluded from the analysis for the propofol Cp50 because the measured whole-blood propofol concentration or the measured plasma fentanyl concentration at 7 min was not within ±35% of the 10-min sample. Of these 56 patients 16 received propofol only. The Cp50 determined from the patients receiving only propofol was 3.3 µg/ml (fig. 3). The Cp50 for prevention of response to verbal command (Cp95) was 5.4 µg/ml. Increasing fentanyl concentrations reduced the Cp50 (P = 0.03), and a fentanyl concentration of 3 ng/ml decreased the propofol Cp50 by approximately 40% (fig. 4). When patients receiving either propofol alone, or propofol and fentanyl were considered for loss of response to a verbal command there was a significant effect of age (P = 0.04). Derived from the model, the propofol Cp50 administered alone was 4.9 µg/ml for a 20-yr-old person, 3.9 µg/ml for a 30-yr-old, and 3.1 µg/ml (fig. 4) for a 40-yr-old.

Concentrations for Prevention of Response to Skin Incision

For the determination of propofol Cp50, 53 patients were used. 17 patients were excluded because the pre- and postincision propofol or fentanyl concentrations were not within 35% of each other. The measured plasma fentanyl concentrations again tended to be higher than that predicted by CACI, ranging from 0 to 6.6 ng/ml. The propofol whole-blood concentrations ranged from 0.42 to 33.3 µg/ml. CACI maintained the pre- and postincision propofol and fentanyl concentrations constant during this period.

The Cp50 for propofol alone, calculated from the patients receiving only propofol, was 15.2 µg/ml (95% confidence interval 7.6, 22.8) (fig. 5). The propofol Cp50 for prevention of response to skin incision (Cp50i) was 27.4 µg/ml. The reduction of propofol Cp50 by fentanyl was highly significant (P < 0.01) and is shown in figure 6. Based on this model which included patients both receiving and not receiving fentanyl the Cp50i for propofol alone was slightly lower at 13.9 µg/ml propofol. A plasma fentanyl concentration of 1 ng/ml resulted in a 63% reduction of the propofol Cp50i. Increasing the plasma fentanyl concentration to 3 ng/
ml results in an 89% reduction in the propofol Cp50i. Increasing the fentanyl concentration beyond 3 ng/ml produced proportionally a much smaller reduction in Cp50i, demonstrating a ceiling effect. A 50% reduction in the Cp50i was provided by a fentanyl concentration of 0.63 ng/ml.

**Discussion**

The first aim of this study was to establish (at pseudo-steady state) arterial whole-blood propofol concentrations at two clinically important and measurable end points: loss of response to a verbal command (Cp50i) and loss of response (purposeful movement) at skin incision (Cp50i). The Cp50i for propofol alone was 3.3 μg/ml and for skin incision was 15.2 μg/ml. The second aim was to determine the reduction by fentanyl or the interaction between propofol and fentanyl for the Cp50i and Cp50i. Fentanyl decreased the propofol Cp50i (P = 0.03), with 3 ng/ml fentanyl reducing the Cp50i by approximately 40%. Increasing fentanyl concentrations markedly decreased the propofol Cp50i with 3 ng/ml providing a nearly 90% reduction in the Cp50i. Propofol and fentanyl were given using a pharmacokinetic model-driven CACI system, such that equilibrium between blood concentrations and their theoretical effect compartment was obtained at the time drug effect was assessed.

A variety of techniques have been used to establish the dose and plasma concentration of propofol necessary to induce loss of consciousness. Techniques...

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Fig. 5. Propofol concentration at which patients did respond (movement) (filled circles) and did not respond (no movement) (open circles) to skin incision when only propofol was administered. The concentration at which 50% of patient did not respond to incision (Cp50i) was 15.2 μg/ml (95% confidence interval 7.6, 22.8).

Fig. 6. Reduction by increasing concentrations of fentanyl of propofol concentration at which 50% or 95% of patients did not move at skin incision (Cp50i and Cp95, respectively). Solid lines = logistic regression solution.
have included administration of a single bolus dose of propofol and the sampling of blood for propofol the moment the patient regains consciousness. Other techniques involve infusion of propofol at a fixed infusion rate and the sampling of blood for propofol at loss of consciousness, or use of infusions to deliver increasing amounts of propofol in small increments until loss of consciousness occurs. A bolus dose of any drug given intravenously will demonstrate hysteresis, where the measured effect (in this case loss of consciousness), as determined by the effect site concentration, lags behind the measured plasma concentration of the drug. The degree of hysteresis is reflected by the half-time for equilibration between blood and brain, which for propofol is $2.9 \pm 2.2$ min. We gave propofol to a target concentration which was maintained for 10 min before assessing patients’ consciousness level. This represents a sufficient period of time to allow 95% equilibration between plasma and effect site concentration. Arterial blood sampling at 7 and 10 min for whole-blood propofol concentrations was performed to demonstrate that the desired target whole-blood concentrations of propofol had been achieved and remained steady for 3 min before when the assessment for loss of consciousness was made. Ideally, whole-blood propofol concentrations at 7 and 10 min should be identical to accurately model concentration to effect.

We considered all patients whose 7- and 10-min whole-blood propofol concentrations were within ± 35% to be acceptable for inclusion in this study. We chose this degree of variability prospectively: it represents the median performance error of our CACI device with the pharmacokinetic values we used. We were able to maintain reasonably constant blood concentrations in the majority of the patients. We have used this degree of variability in other studies establishing concentration–effect relations. Arterial blood sampling was performed because venous samples have been shown to be unreliable.

Propofol concentrations on awakening have been quoted at 1.0–2.19 µg/ml. These values may not be accurate because they were measured after bolus dosing, in the presence of other drugs, or from venous samples. More recently, Vuyk et al., using small-step incremental infusion, which limited the degree of hysteresis, used arterial blood samples to establish the propofol CP50 as 3.4 µg/ml and the CP90s as 4.3 µg/ml. Our results for propofol CP50 of 3.3 µg/ml and the CP95s of 5.4 µg/ml correspond very closely with their findings. From both our study and the results of Vuyk et al., an effect compartment concentration of 4.5–6.5 µg/ml propofol should be chosen to induce loss of consciousness (i.e., CP95 in young healthy patients).

When assessing the reduction of propofol CP50s by fentanyl, because the half-time for equilibration between blood and brain for fentanyl is $6.4 \pm 1.3$ min, we had to “overpressure” the fentanyl infusion for the first 2 min by programming the CACI device to target a desired plasma fentanyl concentration of 1.5 times the actual plasma fentanyl concentration required so as to achieve equilibrium between plasma and the effect compartment at 10 min when loss of consciousness was assessed.

Moffat et al. observed that treating patients with 1 µg/kg of fentanyl or 5 µg/kg of alfentanil did not significantly alter the induction dose of propofol. Others have shown that bolus doses of fentanyl reduce thiopental requirements to produce loss of consciousness. However, when steady bi-phase concentrations of thiopental were combined with plasma fentanyl concentrations of as great as 2 ng/ml there was no significant reduction seen in the plasma thiopental concentration required to produce hypnosis. Analgesic doses of opioids have also been shown not to alter MAC awake of isoflurane and halothane. Short et al., however, demonstrated that alfentanil, using bolus doses, produced a synergistic interaction with propofol for loss of consciousness. Vinik et al., on the other hand, when combining propofol with alfentanil, showed that alfentanil did not potentiate the hypnotic effects of propofol. Thus, the interaction between opiates and propofol to induce loss of consciousness is controversial. Our data demonstrate a moderate but statistically significant reduction in the propofol CP50s with increasing fentanyl concentrations. The reduction by fentanyl of the propofol CP50s is much less than its reduction of the propofol CP50.

Age is known to influence the requirements of many drugs producing anesthesia. MAC values for the potent volatile anesthetics are altered by age. Studies have demonstrated that the propofol requirements for induction and maintenance of anesthesia are reduced in the elderly. This increased sensitivity to propofol may be explained either by pharmacokinetic differences or pharmacodynamic differences. The volume of the central compartment and total body clearance of

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propofol are lower in the elderly.\textsuperscript{13,28} In our study, using patients aged 20–55 yr, significant reduction of propofol CP\textsubscript{50}, was seen with increasing age (approximately a 20% decrease in propofol concentration for each 10-yr increase in age). As blood concentrations were measured, an increase in brain sensitivity to propofol with increasing age is implied (i.e., these differences are due to a pharmacodynamic effect). This is in contrast to thiopental, where age was not shown to alter the sensitivity of the brain in suppressing the EEG.\textsuperscript{29} Propofol and thiopental appear to have different mechanisms of anesthetizing action, which may explain the differences in the effects of these drugs with increasing age. This difference between thiopental and propofol may also be due to the different measures of effect used in these studies (i.e., loss of response to a verbal command vs. suppression of the EEG).

The whole-blood propofol concentration for the propofol CP\textsubscript{50} was 15.2 μg/ml. The propofol concentrations required to prevent movement to a surgical skin incision are high and demonstrate considerable patient to patient variation. The patient to patient variability may be explained partly by differences in age, partly by differences in incision site, and partly due to the fact that propofol has limited analgesic activity. In a similar study on the MAC reduction of isoflurane by fentanyl we saw a similar variability in the isoflurane MAC.\textsuperscript{5} There are no other clinical studies in humans evaluating propofol requirements during surgery when propofol is given as the sole agent. After a 20–30-mg temazepam premedication, Davidson recently reported the venous CP\textsubscript{50} of propofol alone as 8.1 μg/ml.\textsuperscript{30} Midazolam will reduce the dose of propofol necessary to prevent a response to a tectonic stimulus by 50%.\textsuperscript{22} Thus the interaction with temazepam and the use of venous blood concentrations probably explains why our CP\textsubscript{50} is considerably higher than that measured by Davidson \textit{et al.}\textsuperscript{30} When given in conjunction with 70% nitrous oxide, the propofol concentrations during superficial surgery are in the range of 2.0–5.5 μg/ml.\textsuperscript{10,30,31} The interaction between propofol and nitrous oxide has not yet been elucidated and as this interaction may be synergistic, extrapolation from this data is not possible.

It is generally accepted that the MAC value of potent volatile anesthetics are reduced when combined with opioids.\textsuperscript{1,5,32,33} More recently, these reductions in volatile agent MAC values have been quantified at steady biophase conditions in humans.\textsuperscript{3,32} Plasma fentanyl concentrations of 1.67 ng/ml reduce the MAC of isoflurane by 50%.\textsuperscript{5} Plasma fentanyl concentrations of 3 and 6 ng/ml reduce the MAC of desflurane by 48% and 68%, respectively.\textsuperscript{33} As with earlier studies in dogs,\textsuperscript{34,35} it was found that significantly increasing opioid concentrations did not further reduce MAC.

In investigations of opioid interactions with propofol, studies have used bolus doses of the opioid or steady infusions of opioids and varying propofol infusion rates to surgical and clinical requirements. Few studies have attempted to achieve pseudo–steady-state conditions for both propofol and opioid in the absence of any other drugs. In the presence of 67% nitrous oxide and a morphine premedication, the mean blood propofol concentrations to prevent 50% and 95% of the study population from moving during body surface surgery were 1.76 μg/ml and 3.38 μg/ml.\textsuperscript{36} Substituting a lorazepam premedication in place of the morphine results in higher propofol concentrations of 2.5 and 5.92 μg/ml, respectively.\textsuperscript{31} In a total intravenous anesthetic, combining propofol with fentanyl 15 μg·kg\textsuperscript{-1}·h\textsuperscript{-1} in the presence of a temazepam premedication, propofol CP\textsubscript{50}l and CP\textsubscript{50}i were reported as 1.2 and 4.0 μg/ml for body-surface surgery.\textsuperscript{37} These studies suggest there are significant reductions in the requirements of propofol for surgery in the presence of an opioid.

In this study we found that 1 ng/ml fentanyl reduces the CP\textsubscript{50}l of propofol by 63% to a propofol concentration of 5.2 μg/ml. To provide these concentrations, a loading dose of fentanyl of 3 μg/kg followed by 0.02–0.03 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} as an infusion is combined with propofol 1–1.5 mg/kg followed by a 130–150 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} infusion. 2 ng/ml fentanyl reduces the CP\textsubscript{50}l of propofol to 2.7 μg/ml (an 80% reduction in CP\textsubscript{50}l). A 50% reduction in the CP\textsubscript{50}l is produced by a fentanyl concentration of 0.6 ng/ml fentanyl. This is much smaller than the fentanyl concentration required to produce a 50% reduction in isoflurane MAC. The interaction between fentanyl and propofol in providing anesthesia shows a greater reduction in CP\textsubscript{50}l than the reduction in the MAC of isoflurane by fentanyl.

Increasing the fentanyl plasma concentration above 3 ng/ml does produce further reductions in propofol CP\textsubscript{50}i, but as with the potent volatile agents, further increases in plasma fentanyl concentrations are followed by minimal further reduction in the propofol CP\textsubscript{50}l (i.e., a ceiling effect). Thus the interaction between propofol and fentanyl in providing adequate anesthesia is complex and may well explain episodes of awareness during total intravenous anesthesia with propofol plus an opiate. Fentanyl concentrations be-
yond 3 ng/ml provide very little further reduction in propofol requirements. At 2 ng/ml the \( C_{p50}\) of propofol is very close to the \( C_{p50}\). From these results it may be recommended that if awareness is to be avoided when using a total intravenous anesthetic technique involving propofol, then at minimum, a propofol \( C_{p50}\) and preferably a \( C_{p90}\) whole-blood propofol concentrations must be targeted, even in the presence of analgesic concentrations of fentanyl. Thus it would appear prudent when administering propofol as part of a total intravenous technique that the propofol concentration is maintained at greater than 3.3 ng/ml. This would correspond to a propofol infusion of approximately 80 \( \mu g \cdot kg^{-1} \cdot min^{-1}\). Also, because of the ceiling effect produced with increasing concentrations of fentanyl, it would appear logical in noncardiac procedures, to target a fentanyl concentration of 1.5–3 ng/ml and then administer and titrate the propofol to provide an adequate depth of anesthesia.

In conclusion, we studied the interaction between propofol and fentanyl (when both had equilibrated with their biophase) on loss of consciousness and skin incision. The \( C_{p50}\) for loss of consciousness for propofol alone was 3.3 ng/ml and this was significantly reduced by age and increasing fentanyl concentration. The \( C_{p50}\) for propofol for skin incision was 15.2 ng/ml. This concentration was markedly reduced by the presence of fentanyl. A 50% reduction in the \( C_{p50}\), was produced by a fentanyl concentration of 0.63 ng/ml, higher concentrations of fentanyl (above 3 ng/ml) resulted in a ceiling effect with minimal further reduction in the propofol \( C_{p50}\).

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