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The Pharmacodynamic Interaction between Propofol and Fentanyl with Respect to the Suppression of Somatic or Hemodynamic Responses to Skin Incision, Peritoneum Incision, and Abdominal Wall Retraction

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Background: **Sufficient propofol or fentanyl doses necessary to prevent the response to skin incision do not necessarily attenuate hemodynamic responses during surgery. The goal of this study was to characterize the pharmacodynamic interaction between propofol and fentanyl with respect to the suppression of somatic or hemodynamic responses after three stimuli: skin incision, peritoneum incision, and abdominal wall retraction.**

Methods: **Propofol and fentanyl were administered *via* computer-assisted continuous infusion to provide equilibration between plasma–blood and biophase concentrations. Patients were randomized to nine groups that received predetermined concentrations of fentanyl (from 0 to 9 ng/ml). Each patient was administered different target concentrations of propofol. Somatic and hemodynamic responses were measured before and after each of three different stimulations: skin incision (si), peritoneum incision (pi), and abdominal wall retraction (ret). The propofol plasma concentrations at which 50% of the patients did not respond to each type of stimulation (Cp50si, Cp50pi, and Cp50ret) were calculated by fitting the Loewe synergistic model.**

Results: **For propofol alone, Cp50si, Cp50pi, and Cp50ret were 12.9, 17.1, and 19.4 μg/ml, respectively. Increasing the fentanyl concentration markedly reduced propofol Cp50si, Cp50pi, and Cp50ret for somatic response, indicating the potential synergistic interaction of both drugs. During the prestimulation period, fentanyl did not decrease systolic blood pressure; however, propofol specifically decreased systolic blood pressure. Both drugs had a synergistic drug interaction on the systolic blood pressure increase after various surgical stimulations. Fentanyl and propofol concentrations that suppressed both the 50% probability of somatic response and the 50% probability of moderate hemodynamic change defined by the 15% systolic blood pressure increase over the prestimulation value were 3.6 ng/ml and 2.5 μg/ml for skin incision, 8.4 ng/ml and 1.6 μg/ml for peritoneum incision, and 5.9 ng/ml and 5.1 μg/ml for wall retraction, respectively.**

Conclusions: **The anesthesia requirements for stimuli that are more intense than skin incision should be considered during abdominal surgery. Somatic and hemodynamic responses varied depending on the type of surgical stimuli. (Key words: Anesthetic potency; blood pressure; computers; heart rate; intravenous anesthetics.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 7A.

FOR intravenous anesthetics, the index of potency has been defined in terms of the plasma concentration necessary to prevent a response in 50% (Cp50) and 95% (Cp95) of patients to stimulation by skin incision, and this index is a guide for therapeutic concentrations.[1-3] However, the intensity of stimulation varies during surgery with different types of stimuli. Ideally, the anesthetic infusion rate should be adjusted in each patient according to the expected intensity of an impending stimulation, and the plasma concentrations should be maintained at slightly more than the minimum level necessary to maintain satisfactory anesthetic conditions to allow rapid recovery[4-6] and stable hemodynamic conditions. The alfentanil requirement to suppress a somatic or hemodynamic response is more for a peritoneum incision than for a skin incision.[7,8]

Recently, we described the pharmacodynamic interaction between propofol and fentanyl needed to suppress responses to the perioperative stimuli of verbal command, tetanic stimulation, laryngoscopy, tracheal intubation, and skin incision.[9] Empirically, often there are marked increases in blood pressure during the early

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phase of abdominal surgery, even in patients who are administered doses more than the Cp95 for skin incision during propofol and fentanyl anesthesia. Ausems *et al.*[1] reported that skin incision is not the most intense stimulus in the perioperative period. We hypothesized that peritoneum incision and abdominal wall retraction may be more intense stimulations than skin incision and that the hemodynamic response may be different than the somatic response in each of these situations. However, the propofol plasma concentration necessary for peritoneum incision and abdominal wall retraction and the effects on somatic response to these stimuli by the interaction of fentanyl with propofol have not been investigated precisely; nor have specific hemodynamic responses been assessed. To maintain anesthesia when using propofol and fentanyl, it is important to establish the therapeutic concentrations necessary to limit the response during various surgical conditions.

This study was designed (1) to determine the plasma propofol concentration at which 50% and 95% of patients do not respond somatically to skin incision (Cp50si, Cp95si), peritoneum incision (Cp50pi, Cp95pi), or abdominal wall retraction (Cp50ret, Cp95ret); (2) to measure the reduction of Cp50si, Cp50pi, and Cp50ret by the addition of fentanyl when both drugs have reached a steady biophase concentration; and (3) to observe the interaction of the propofol and fentanyl concentration on hemodynamic responses to three different stimuli: skin incision, peritoneum incision, and abdominal wall retraction.

Materials and Methods

After approval from the District Ethics Committee of Hamamatsu University Hospital, 99 patients were chosen who were classified as American Society of Anesthesiologists physical status 1 or 2 and were scheduled for elective surgery involving gastric resection. After we explained the study, each patient provided informed consent. Patients who were significantly obese (body mass index > 30); those with known cardiac, pulmonary, liver, renal, or metabolic diseases; and those who were receiving medications were excluded from the study.

Stable blood concentrations of propofol and fentanyl were achieved using a pharmacokinetic model-driven infusion device designed for computer-assisted continuous infusion. The system consists of a microcomputer interfaced to an ATOM syringe pump (NEC 9821 computer, NEC, Tokyo Japan; model 1235 syringe pump, ATOM, Tokyo, Japan) using a three-compartment model with central elimination. The control software was programmed in the Turbo Pascal language (Borland International, Scotts Valley, CA) by one of the authors. The pharmacokinetic parameters used for computer-assisted continuous infusion for fentanyl and propofol were reported previously by and Gepts[10] and Shafer.[11]

For each pair of predicted and measured values, the prediction error and absolute prediction error[12] expressed as a percentage was given by

$$\text{Prediction error} = \frac{\text{Cp (measured)} - \text{Cp (predicted)}}{\text{Cp (predicted)}} \times 100$$

$$\text{Absolute prediction error} = \frac{|\text{Cp (measured)} - \text{CP (predicted)}|}{\text{Cp (predicted)}} \times 100$$

The median prediction error and the median absolute prediction error were calculated.

Clinical Protocol

One day before surgery, a central venous catheter was inserted *via* the right jugular vein during regional anesthesia, and it was used for propofol and fentanyl administration during anesthesia. Patients were brought to the operating room without administration of premedication. Before induction of anesthesia, a peripheral venous catheter for fluid replacement and a radial arterial catheter to measure arterial pressure and to sample blood were inserted.

Anesthesia was induced with propofol (main target concentration, 1–3 μg/ml) and various predetermined concentrations of fentanyl. After patient loss of consciousness was verified, tracheal intubation was facilitated by additional increases in the propofol concentration and 1 mg/kg succinylcholine administered intravenously. The patients' lungs were ventilated mechanically with 100% oxygen to normocapnia, and normal body temperature was maintained (35.5 to 37°C) during the study.

The surgeon was asked to perform skin incision, peritoneum incision, and abdominal wall retraction while refraining from use of electrocautery until the patient's responses were determined after each stimulation. The stimulation of abdominal wall retraction was provided with an abdominal retractor, which widened the abdom-

inal cavity to maximal exposure. Vecuronium was used only when absolutely necessary to facilitate surgery and only in the smallest dose needed for skin incision, peritoneum incision, or abdominal retraction. The degree of muscular blockage was estimated every 5 min by integrated electromyography (RELAXOGRAPH, DATEX, Helsinki, Finland). We maintained the T1:T4 ratio by train-of-four monitoring at more than 50%.

Assessment of the Response to Surgical Stimulation

Inadequate anesthesia during each of the three stimuli was defined by the following criteria:[13]

- presence of somatic responses, including bodily movements, swallowing, coughing, grimacing, or eye opening;
- an increase in the systemic systolic blood pressure (sBP) more than 15 mmHg above normal levels (normal sBP for each patient was determined from measurements made before surgery in the ward);
- a heart rate (HR) of more than 90 beats/min in the absence of hypovolemia;
- presence of other autonomic signs of inadequate anesthesia, such as lacrimation, flushing, or sweating.

Any movement was noted that occurred during the 60 s after each of the three surgical stimulations. In all patients, somatic responses were assessed by the same attending anesthesiologist and the same assistant resident anesthesiologist, who were both blinded to the selected target concentration or hemodynamic response. Both anesthesiologists were familiar with the strict definition of responses and were continuously looking for any hint of inadequate anesthesia.

Before surgery, the sBP and HR values obtained while patients were resting in the ward were recorded as preanesthesia baseline values. For each patient, continuous measurements of sBP and HR for the 2 min before skin incision were recorded, and the means were calculated as presurgical baselines. For poststimulation values, the maximum measurements during the 2 min after each stimulation were recorded.

Testing Concentrations of Propofol and Fentanyl

Patients were allocated randomly to receive either no fentanyl or predetermined target plasma concentrations of fentanyl at 0.5, 1, 2, 3, 5, 7, 8, or 9 ng/ml (groups 1–9), and these levels were maintained throughout the experimental period. A minimum of 30 min was allocated between the start of the fentanyl infusion and making the skin incision. To assess patient response to skin incision, propofol (from 1–24 μg/ml) was administered at values preselected according to a randomization schedule in each fentanyl concentration group (fig. 1). This range was chosen based on a previous report concerning the effect of fentanyl on the Cp50si for propofol,[3] and propofol concentrations less than induction values were not tested. When the somatic response to skin incision was negative without persistent hypertension, the target concentration of propofol was not changed. When a positive somatic response was observed, the target concentration of propofol was increased immediately by 10, 7, 4, 3, 2, 2, 2, 1, and 1 μg/ml in groups 1–9, respectively. As a consequence, patients received target concentrations of propofol ranging from 1 to 25 μg/ml for peritoneum incision (fig. 1). Depending on the somatic response to the peritoneum incision, the propofol concentration was determined in the same manner as that for skin incision. As a consequence, patients within each group received target concentrations of propofol ranging from 1–28 μg/ml before abdominal retraction (fig. 1). The propofol concentration was maintained for at least 15 min before each stimulation to ensure equilibration between plasma and the effect site.

When a condition of inadequate anesthesia was not alleviated by the propofol infusion defined by the protocol described, it was readily controlled by further increasing the target concentration of propofol. If hypotension occurred at any time, patient blood pressure was restored by a combination of fluid administration and ephedrine as needed. Bradycardia (<50 beats/min) was treated with atropine (0.25 mg administered intravenously).

Measurement of Propofol and Fentanyl

After equilibration of propofol between blood and the effect site, blood samples for analysis of the plasma propofol and plasma fentanyl concentrations were obtained approximately 3 min before and just after stimulation. Only paired samples that had concentrations within ±30% of each other were included. The means of these values were used to obtain Cp50. Plasma samples for propofol were kept on ice and stored at 5°C until extraction and assay. They were assayed within 5 days after sampling. Plasma concentrations of propofol were determined using high-performance liquid chromatography with fluorescence detection at 310 nm after excitation at 276 nm (CTO-10A, RF550, and C-R7A, Shimadsu, Kyoto, Japan).[14] For each batch of plasma samples (for each patient), a separate standard curve was computed

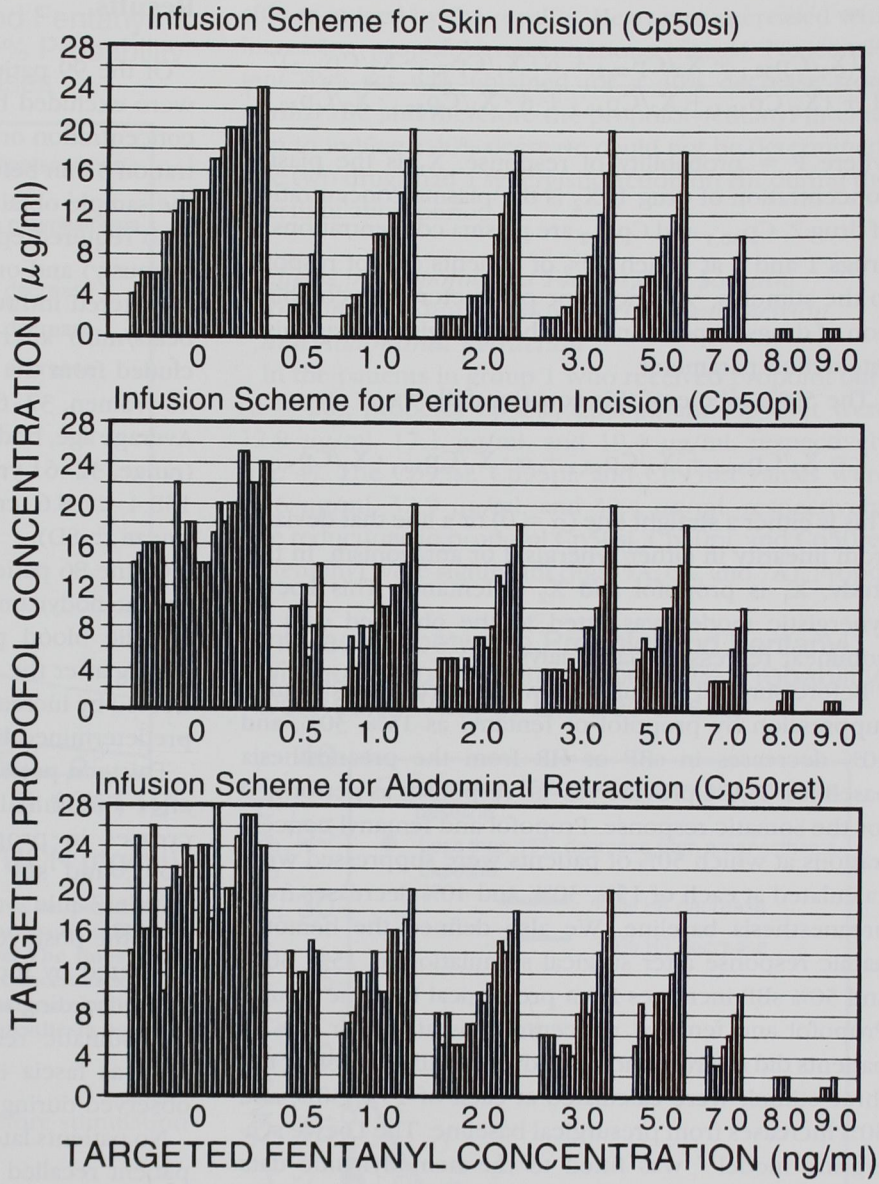

Fig. 1. Target concentrations of propofol and fentanyl to which patients were randomized for assessment of skin incision (Cp50si), peritoneum incision (Cp50pi), and abdominal wall retraction (Cp50ret).

by adding pure propofol liquid to drug-free human plasma to reach concentrations of 1, 5, 10, and 25 μg/ml. Linear regression analysis (least squares) was used with the plasma propofol concentration as the dependent variable. Propofol concentrations in this study were calculated using the obtained regression equation. The lower limit of detection was 32 ng/ml, and the coefficient of variation was 9.5%.

The blood samples for determining plasma fentanyl concentration were immediately placed on ice and the plasma was separated and frozen at −70°C until assay. The plasma concentration of fentanyl was measured by gas chromatography mass spectrometry (model 5989, Hewlett-Packard, Palo Alto, CA) at another laboratory. The lower limit of detection was 0.2 ng/ml, and the interbatch coefficient of variation of the assay over the concentration range in this study was 8.1%.

Statistical Analysis

The interaction between propofol and fentanyl to suppress the somatic responses to these stimuli was evaluated for each stimulus separately by the Loewe synergistic model of drug interaction model:[15]

$$P = \frac{(X_1/Cp_{50,1} + X_2/Cp_{50,2} + \alpha \cdot X_1/Cp_{50,1} \cdot X_2/Cp_{50,2})^{\gamma}}{1 + (X_1/Cp_{50,1} + X_2/Cp_{50,2} + \alpha \cdot X_1/Cp_{50,1} \cdot X_2/Cp_{50,2})^{\gamma}}$$

where P = probability of response, X_1 is the plasma concentration of drug 1, X_2 is the plasma concentration of drug 2, $Cp_{50,1}$ and $Cp_{50,2}$ are plasma concentrations of drugs 1 and 2 at which 50% of patients do not respond to the stimulus, γ is the slope parameter for a combination of drugs 1 and 2, and α is the synergism–antagonism interaction parameter.

The 50% isobole of this equation follows:

$$1 = X_1/Cp_{50,1} + X_2/Cp_{50,2} + \alpha \cdot X_1/Cp_{50,1} \cdot X_2/Cp_{50,2}$$

This is either a straight line ($\alpha = 0$) or a line that deviates from linearity in either synergism or antagonism. In this study, X_1 is propofol and X_2 is fentanyl. This Loewe synergistic model was fitted to the obtained data by nonlinear regression data analysis.

Before surgical stimulation, we defined hemodynamic suppression by propofol or fentanyl as 15%, 30%, and 40% decreases in sBP or HR from the preanesthesia baselines. These provide yes–no responses as performed for the somatic response. Propofol and fentanyl concentrations at which 50% of patients were suppressed were calculated at each of 15%, 30%, and 40% decreases from preanesthesia baseline. We also defined the hemodynamic response after surgical stimulation as 15%, 30%, and 50% sBP increases from presurgical baseline values. Propofol and fentanyl concentrations at which 50% of patients did not respond hemodynamically to each of the three stimuli were calculated at each of 15%, 30%, and 50% increases from presurgical baseline. The Loewe synergistic model[15] was fitted to the hemodynamic data obtained during prestimulation and after various surgical stimulations for skin incision, peritoneum incision, and abdominal retraction.

Evaluation of the influence on hemodynamic response with and without surgical stimulation was assessed by multiple regression analysis of the following parameters: somatic response, other autonomic responses, plasma propofol concentration, and plasma fentanyl concentration. The somatic or other autonomic responses were expressed as 1 for reaction and as 0 for absence of reaction. Statistical analysis was conducted using statistical software (Statview 4.0, Abacus Concepts, Berkeley, CA). Statistical significance was established at $P < 0.05$.

Results

Of the 99 patients who participated in this study, 10 were excluded because the measured plasma propofol concentration or the measured plasma–fentanyl concentration 3 min before stimulation was not within ±30% of the sample obtained just after stimulation. Two patients who required ephedrine (4 to 8 mg administered intravenously) and one who required atropine (0.25 mg administered intravenously) because of bradycardia (<50 beats/min) after the fentanyl infusion were also excluded from the study. Eighty-six patients (46 men and 40 women, 32–61 yr old) were included in the analysis. Average age, body weight, and height were 53.9 ± 9.6 yr (range, 32–61 yr), 51.7 ± 9.3 kg (range, 46–79 kg), and 158.4 ± 8.6 cm (range, 146–175 cm), respectively (mean ± SD).

Of the 86 patients assessed in this study, 6 had excessive hemodynamic reactions to the peritoneum incision. Systolic blood pressure increased to more than 170 mmHg after the peritoneum incision. The patients were treated by increases in the target propofol concentration predetermined by the protocol.

Thirteen patients had excessive high blood pressure after abdominal retraction. They were treated by increases in propofol and fentanyl target concentrations, and sBP decreased to less than 170 mmHg within 3 min.

All the positive somatic responses to stimulation were alleviated by increasing the target propofol concentration according to the predetermined protocol. No positive somatic responses to other surgical stimulation, such as fascia incision or hemostatic clamping, were observed during the study.

No patients later indicated awareness, in as much as no patient recalled any event occurring during this study, when questioned at a 24-h postoperative visit. No other adverse effects occurred during this study. Blood gas levels and hemoglobin concentrations did not change significantly; rectal temperature decreased slightly from 36.7 ± 0.6°C at the beginning to 36.3 ± 0.7°C at the end of the measurement period. The median prediction error and the median absolute prediction error for computer-assisted continuous infusion administration of propofol were −5.3% and 24.9%, respectively. The median prediction error and the median absolute prediction error for computer-assisted continuous infusion administration of fentanyl were 37.9% and 42.9%, respectively. During this study, the average value of the T1:T4 ratio by

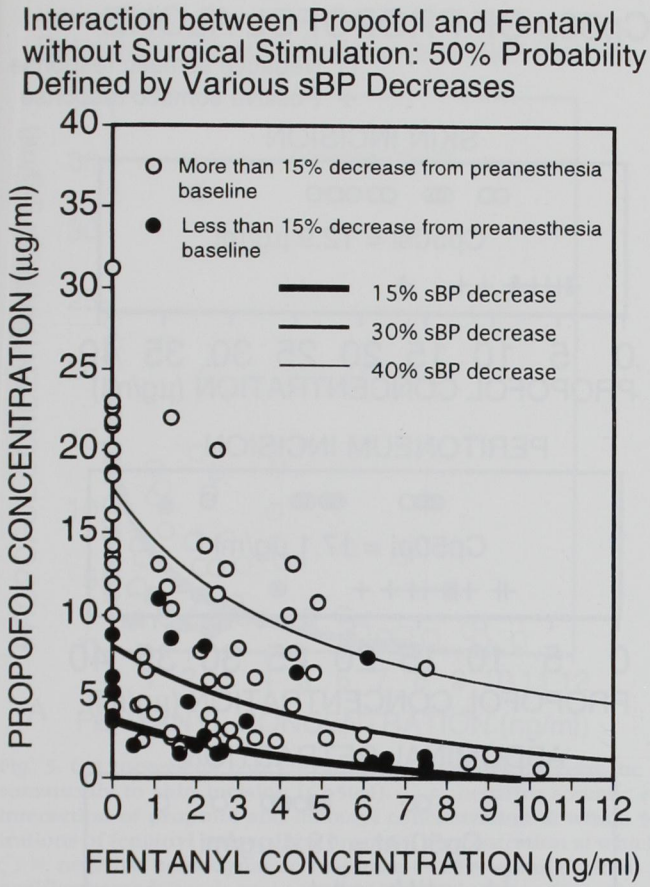

Fig. 2. Open and closed circles show negative or positive responses defined by a 15% systolic blood pressure (sBP) decrease from the preanesthesia baseline value. The lines show the interaction of propofol and fentanyl concentrations at which 50% of patients did not respond hemodynamically with a 15%, 30%, or 40% sBP decrease from preanesthesia baseline values.

the train-of-four method was 61 ± 9% before stimulation and 63 ± 13% after stimulation.

Hemodynamic Response to the Interaction of Propofol and Fentanyl without Surgical Stimulation

Figures 2 and 3 show the propofol and fentanyl concentrations at which 50% of patients did not respond hemodynamically by showing various sBP and HR decreases without surgical stimulation. Without fentanyl, 15%, 30%, and 40% decreases from normal sBP were provided by 3.6, 8.1, and 17.7 μg/ml of propofol in 50% of patients. The sBP was decreased mainly by propofol during the prestimulation period (table 1), and this decrease was dose dependent (table 2, fig. 2). Propofol combined with fentanyl exerts a synergistic effect on sBP, as judged by the α value. Heart rate decreased with increasing propofol concentrations (fig. 3). No consistent data set was obtained for a 40% decrease from normal HR, and therefore the propofol–fentanyl interaction to induce a 40% decrease could not be determined. The two drugs had a synergistic action on HR during the prestimulation period.

Effects of Propofol and Fentanyl on Somatic Response to Skin Incision, Peritoneum Incision, and Abdominal Retraction

In the patients in group 1 who received propofol only (n = 26), propofol Cp50si, Cp50pi, and Cp50ret were 12.9 μg/ml, 17.1 μg/ml, and 19.4 μg/ml, respectively (fig. 4). The Cp95si, Cp95pi, and Cp95ret values were 26.6 μg/ml, 32.9 μg/ml, and 32.4 μg/ml, respectively. The reductions in propofol Cp50si, Cp50pi, and Cp50ret by fentanyl were significant (figs. 5A, 6A, and 7A). Propo-

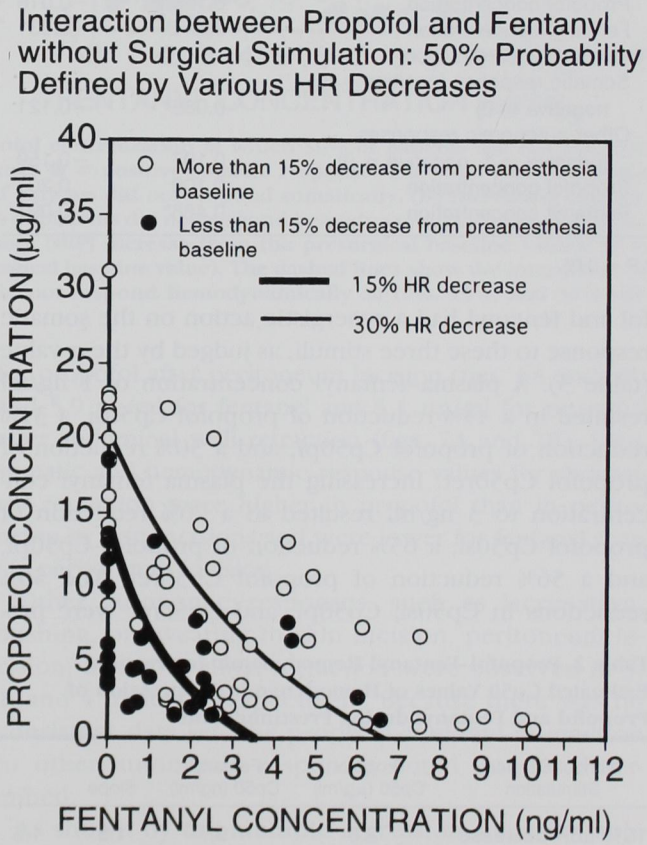

Fig. 3. Open and closed circles show negative or positive responses defined by 15% heart rate (HR) decrease from preanesthesia baseline values. The lines show the interaction of propofol and fentanyl concentrations at which 50% of patients did not respond hemodynamically with a 15% or 30% HR decrease from preanesthesia baseline values.

Table 1. Results of Multiple Regression Analysis Evaluation of the Influence of the Somatic Response, Other Autonomic Responses, Propofol Concentration, and Fentanyl Concentration on Systolic Blood Pressure and Heart Rate

Effect to Be Tested by Multiple Regression	Correlation Coefficient	
	Blood Pressure	Heart Rate
Without surgical stimulation		
Propofol concentration	0.494*	0.212
Fentanyl concentration	0.074	0.501*
Skin incision		
Somatic response (positive = 1, negative = 0)	0.459*	0.136
Other autonomic responses (positive = 1, negative = 0)	0.107	0.071
Propofol concentration	0.015	0.021
Fentanyl concentrations	−0.417*	−0.103
Peritoneum incision		
Somatic response (positive = 1, negative = 0)	0.288*	0.061
Other autonomic responses (positive = 1, negative = 0)	0.122	−0.075
Propofol concentration	0.135	−0.016
Fentanyl concentration	−0.644*	−0.031
Abdominal wall retraction		
Somatic response (positive = 1, negative = 0)	0.085	−0.121
Other autonomic responses (positive = 1, negative = 0)	0.197	−0.159
Propofol concentration	0.100	0.203
Fentanyl concentration	−0.466*	−0.097

* $P < 0.05$.

fol and fentanyl had a synergistic action on the somatic response to these three stimuli, as judged by the α value (table 3). A plasma-fentanyl concentration of 1 ng/ml resulted in a 44% reduction of propofol Cp50si, a 31% reduction of propofol Cp50pi, and a 30% reduction of propofol Cp50ret. Increasing the plasma fentanyl concentration to 3 ng/ml resulted in a 76% reduction of propofol Cp50si, a 65% reduction of propofol Cp50pi, and a 56% reduction of propofol Cp50ret. The 50% reductions in Cp50si, Cp50pi, and Cp50ret were provided by fentanyl concentrations of 1.2, 1.8, and 2.8 ng/ml, respectively.

Table 2. Propofol–Fentanyl Hemodynamic Interaction; Estimated Cp50 Values of Hemodynamic Suppression of Propofol and Fentanyl during Prestimulation

Without Surgical Stimulation	Propofol Cp50 (μg/ml)	Fentanyl Cp50 (ng/ml)	Slope	α
15% sBP decrease	3.6	9.7	1.5	1.5
30% sBP decrease	8.1	20.5	1.6	3.1
40% sBP decrease	17.7	195.1	8.5	41.5
15% HR decrease	14.4	3.5	3.3	1.65
30% HR decrease	20.5	6.7	4.6	1.2

sBP = systolic blood pressure; HR = heart rate.

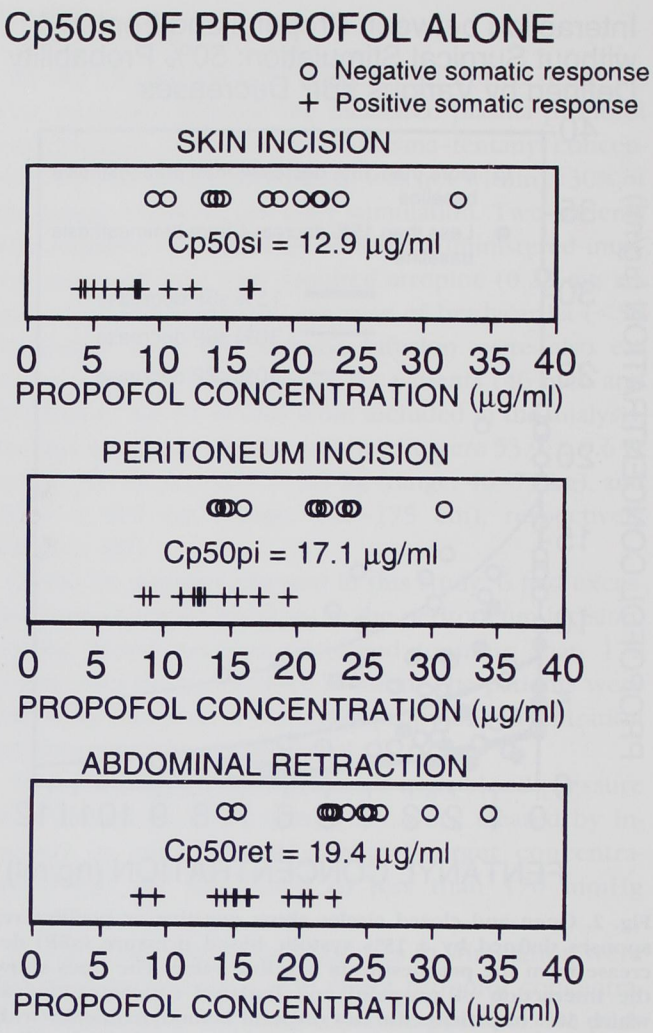

Fig. 4. Propofol concentrations at which patients did and did not respond somatically to skin incision, peritoneum incision, and abdominal wall retraction when only propofol was administered.

Effects of Propofol and Fentanyl on Hemodynamic Response to Skin Incision, Peritoneum Incision, and Abdominal Retraction

The individual hemodynamic responses defined by a 15% increase from prestimulation sBP are shown in figures 5B (skin incision), 6B (peritoneum incision), and 7B (abdominal retraction). The propofol-fentanyl interactions to suppress the sBP increase after various surgical stimulations are shown by 15%, 30%, and 50% sBP increase. No consistent data set of propofol-fentanyl interaction on sBP increase was obtained for 50% sBP in-

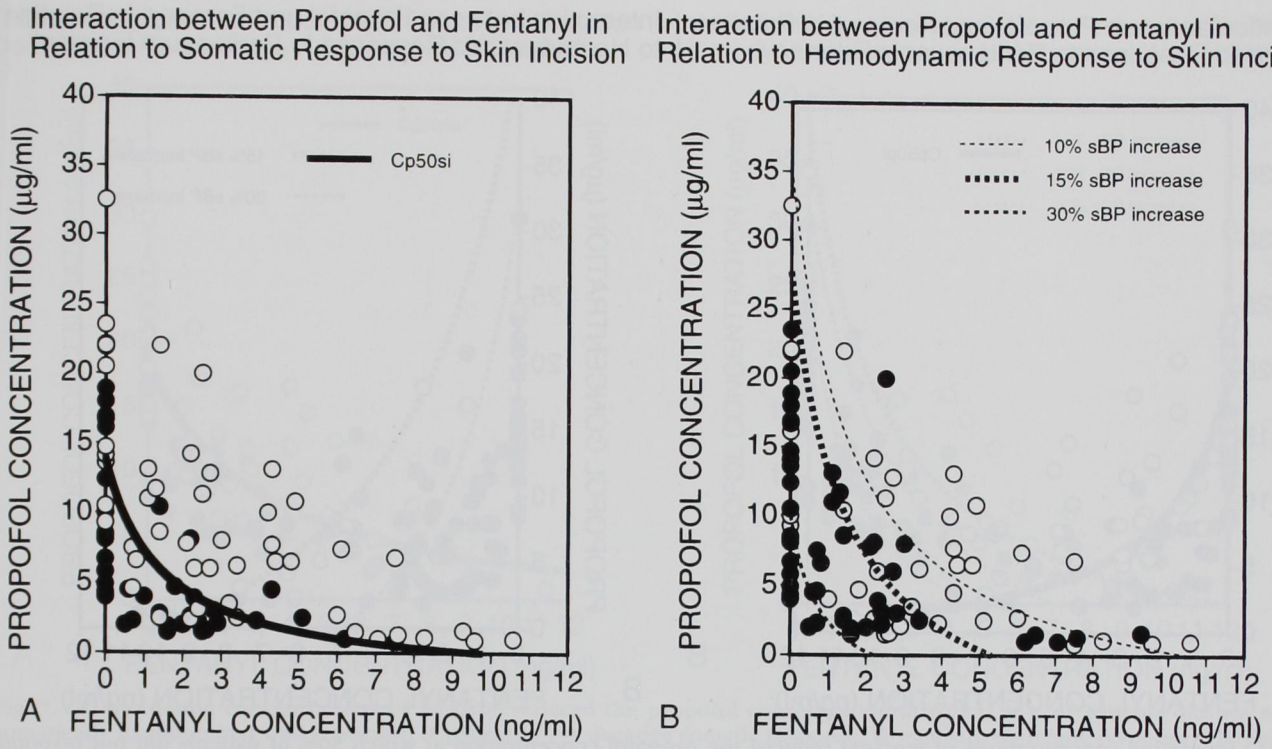

Fig. 5. (*A*) Increasing concentrations of fentanyl reduced the propofol concentration at which 50% of patients did not respond somatically to skin incision (Cp50si). ○ = negative somatic response; ● = positive somatic response. The solid line shows the interaction of propofol and fentanyl concentration at which 50% of patients did not respond somatically. (*B*) Increasing concentrations of fentanyl reduced the propofol concentration at which 50% of patients did not respond hemodynamically to skin incision. ○ = negative hemodynamic response (<15% systolic blood pressure [sBP] increase from the presurgical baseline value); ● = positive hemodynamic response (>15% sBP increase from the presurgical baseline value). The dashed lines show the interaction of propofol and fentanyl concentrations at which 50% of patients did not respond hemodynamically at 10%, 15%, and 30% sBP increases from presurgical baseline values.

crease responses to skin incision and peritoneum incision. Propofol and fentanyl had a synergistic action on the suppression of sBP increase after surgical stimulation (table 3 and figs. 5B, 6B, and 7B). The hemodynamic responses to peritoneum incision and abdominal retraction were higher than those to skin incision. Estimated propofol Cp50 values of hemodynamic response to peritoneum incision were higher than those of skin incision or abdominal retraction (table 3). Estimated fentanyl Cp50 values of hemodynamic responses to peritoneum incision were higher than those to skin incision and were lower than those to abdominal retraction (table 3).

When the hemodynamic response was defined by a 15% sBP increase to surgical stimuli, equisomatic and hemodynamic response values (the 50% probability to suppress somatic and hemodynamic response) after skin incision were at concentrations of 3.7 ng/ml for fentanyl and 2.3 μg/ml for propofol (figs. 5A and 5B). The concentrations were 8.4 ng/ml for fentanyl and 1.6 μg/ml for propofol after peritoneum incision (figs. 6A and 6B) and 5.9 ng/ml for fentanyl and 5.1 μg/ml for propofol after abdominal wall retraction (figs. 7A and 7B). Equisomatic and hemodynamic response values for abdominal retraction were higher in propofol than in peritoneum or skin incisions and were lower for fentanyl than for peritoneum incision.

Other autonomic responses, such as lacrimation, flushing, or sweating to skin incision, peritoneum incision, and abdominal retraction were observed in 3, 4, and 4 patients, respectively. Because there was no consistent data set, the propofol–fentanyl interaction to other autonomic responses could not be determined.

As shown by the multiple regression analysis (table 4), a somatic response to skin incision correlated significantly with fentanyl concentration. The somatic response to peritoneum incision correlated significantly with propofol and fentanyl concentrations. Abdominal retraction correlated significantly with propo-

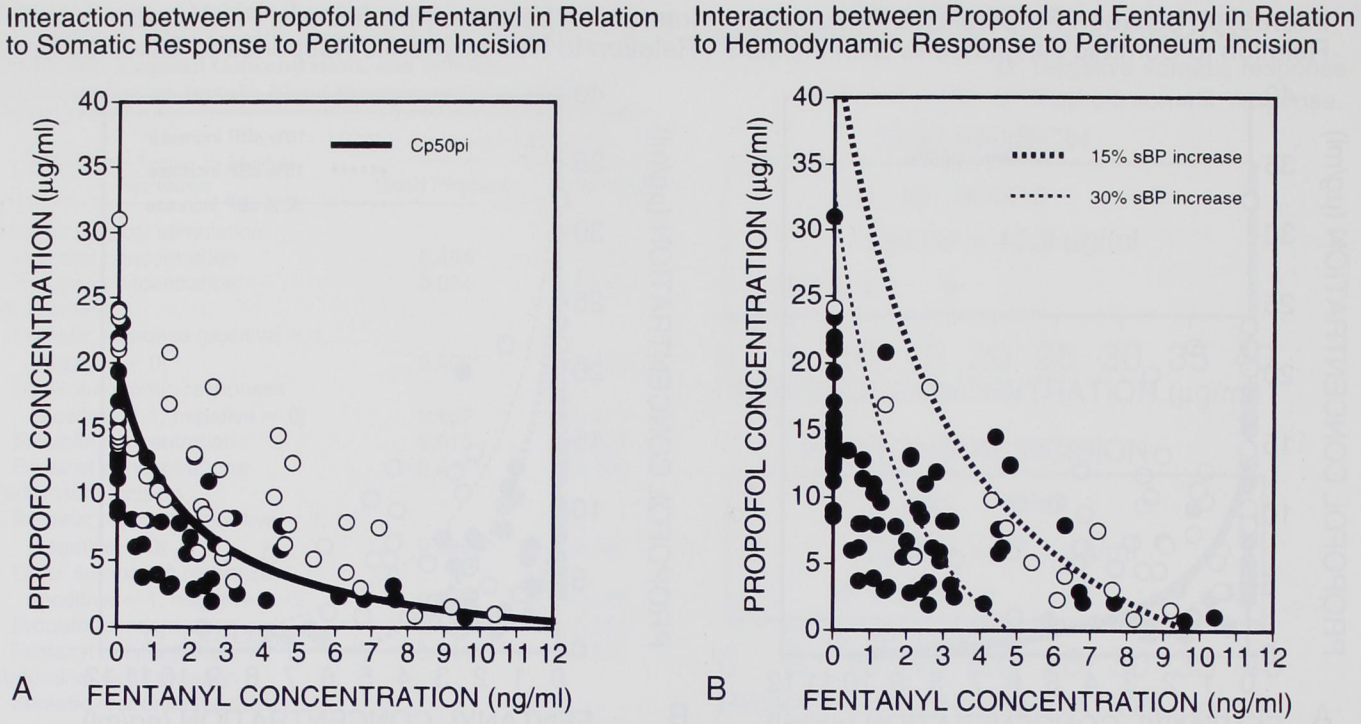

Fig. 6. (*A*) Increasing concentrations of fentanyl reduced the propofol concentration at which 50% of patients did not respond somatically to peritoneum incision (Cp50pi). ○ = negative somatic response; ● = positive somatic response. The solid line shows the interaction of the propofol and fentanyl concentration at which 50% of patients did not respond somatically. (*B*) Increasing concentrations of fentanyl reduced the propofol concentration at which 50% of patients did not respond hemodynamically to peritoneum incision. ○ = negative hemodynamic response (<15% systolic blood pressure [sBP] increase from the presurgical baseline value); ● = positive hemodynamic response (>15% sBP increase from the presurgical baseline value). Dashed lines show the interaction of propofol and fentanyl concentrations at which 50% of patients did not respond hemodynamically at 10%, 15%, and 30% sBP increases from presurgical baseline values.

fol concentration. For hemodynamic responses (table 1), decreases in sBP compared with presurgical stimulation values related significantly to the propofol concentration, and decreases in HR compared with presurgical values correlated with fentanyl concentration. Increases in blood pressure after skin incision or peritoneum incision were closely related to plasma fentanyl concentration and somatic responses. The sBP increase after abdominal retraction did not correlate significantly with somatic response, but fentanyl concentration did. The plasma propofol concentration did not correlate with the sBP increase after skin incision, peritoneum incision, or abdominal retraction (table 4). Other autonomic responses did not correlate with increases in sBP or HR.

Discussion

The goal of this study was to characterize the pharmacodynamic interaction between propofol and fentanyl with respect to the suppression of somatic or hemodynamic responses after three different stimuli: skin incision, peritoneum incision, or abdominal wall retraction. The interaction between these agents can be determined accurately only when data are obtained after blood and effect-site equilibration of propofol and fentanyl and when the blood fentanyl concentration remains constant during the study. The blood and effect-site equilibration half-time of propofol is short (2.9 min).§ In our study, the propofol concentration was maintained for at least 15 min before each stimulation to ensure equilibration between plasma and the effect-site. The predetermined target fentanyl concentration was maintained 30 min before skin incision. For all 86 patients who participated in this study, the measured plasma propofol or fentanyl concentra-

§Schuttler J, Schwilden H, Stoeckel H: Pharmacokinetic-dynamic modeling of Diprivan. ANESTHESIOLOGY 1986; 65:A549

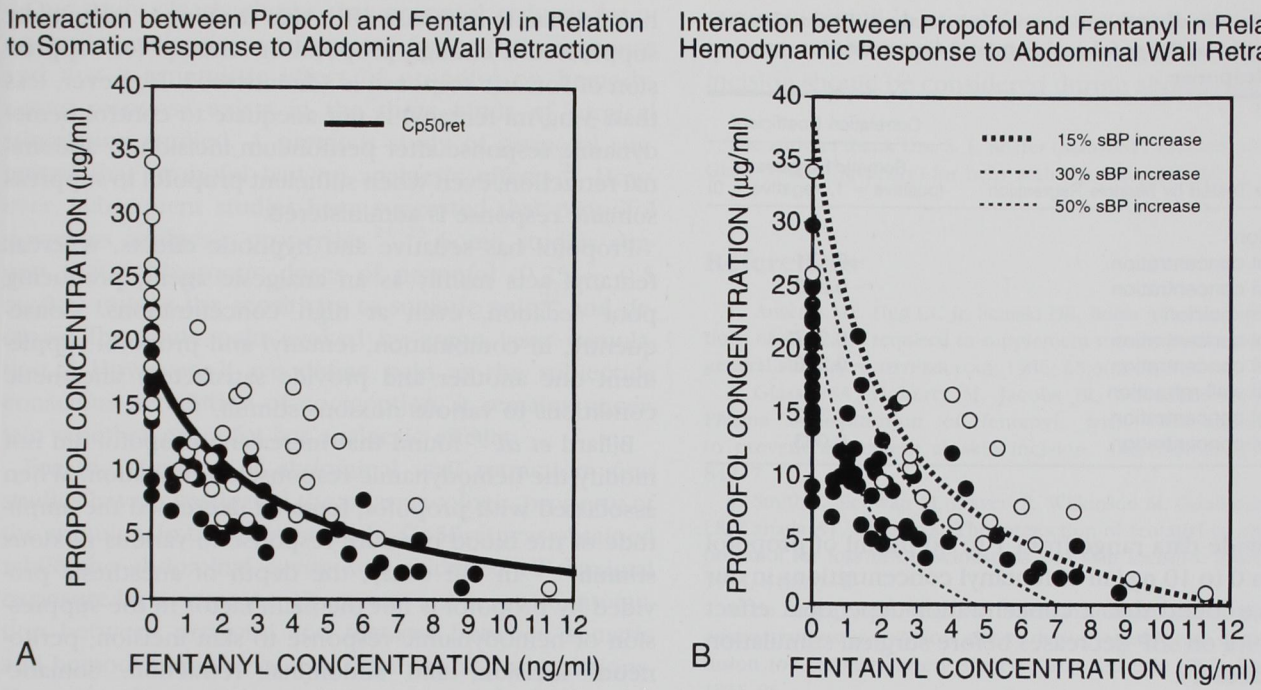

Fig. 7. (*A*) Increasing concentrations of fentanyl reduced the propofol concentration at which 50% of patients did not respond somatically to abdominal wall retraction (Cp50ret). ○ = negative somatic response; ● = positive somatic response. The solid line shows the interaction of propofol and fentanyl concentration at which 50% of patients did not respond somatically. (*B*) Increasing concentrations of fentanyl reduced the propofol concentration at which 50% of patients did not respond hemodynamically to abdominal wall retraction. ○ = negative hemodynamic response (<15% sBP increase from the presurgical baselines); ● = positive hemodynamic response (>15% systolic blood pressure [sBP] increase from the presurgical baseline). The dashed lines show the interaction of propofol and fentanyl concentrations at which 50% of patients did not respond hemodynamically at 10%, 15%, and 30% sBP increases from presurgical baseline values.

tion 3 min before stimulation was within ±30% of the sample obtained just after stimulation.

Hemodynamic Response to the Interaction of Propofol and Fentanyl without Surgical Stimulation

Billard *et al.*[16] reported that the propofol-induced postinduction decrease in sBP was not related to the dose of propofol (from 2 to 3.5 mg/kg) and that there was no difference in sBP values between the 2- and 4-μg/kg doses of fentanyl. The peaks of predicted effect-site concentration at corresponding administration in the reported data were from 4 to 7.5 μg/ml for propofol and from 3 to 6 ng/ml for fentanyl. In our study, the concentration range from 4 to 7.5 μg/ml for propofol and from 3 to 6 ng/ml for fentanyl existed between 50% probability lines of 30% sBP decrease and 40% sBP decrease (fig. 2). Our results are consistent with those from a previous study by Billard *et al.*[16] because a 10% change from 30% to 40% in sBP decrease is small. However, by

Table 3. Propofol–Fentanyl Interaction; Estimated Cp50 Values of Hemodynamic and Somatic Responses to Skin Incision, Peritoneum Incision, and Abdominal Wall Retraction

	Propofol Cp50 (μg/ml)	Fentanyl Cp50 (ng/ml)	Slope	α
Somatic response to skin incision	13.8	9.7	−2.63	6.8
Somatic response to peritoneum incision	19.4	15.1	−2.9	8.1
Somatic response to abdominal retraction	18.6	28	−2.9	9.1
15% sBP increase following skin incision	27.7	5.3	−1.7	3.7
15% sBP increase following peritoneum incision	44.3	9.7	−3.8	3.1
15% sBP increase following abdominal retraction	38	12.1	−4.8	5.8

sBP = systolic blood pressure.

Table 4. Results of Multiple Regression Analysis Evaluation of the Influence of Propofol and Fentanyl Concentration on Somatic Response

Effect to be Tested by Multiple Regression	Correlation Coefficient: Somatic Response (positive = 1, negative = 0)
Skin incision	
Propofol concentration	−0.171
Fentanyl concentration	−0.240*
Peritoneum incision	
Propofol concentration	−0.217*
Fentanyl concentration	−0.218*
Abdominal wall retraction	
Propofol concentration	−0.372*
Fentanyl concentration	0.063

* $P < 0.05$.

using a wide data range from 1 to 30 μg/ml of propofol and from 0 to 10 ng/ml of fentanyl concentrations in our study, we found that a concentration-dependent effect of propofol on sBP decreases before surgical stimulation (fig. 2, table 1).

Shafer *et al.*[17] reported that the average blood propofol concentration necessary for major surgery, primarily involving intraabdominal surgery, was 4.05 μg/ml, and the concentration for minor surgery, mainly urologic surgery, was 2.39 μg/ml when 70% of nitrous oxide and meperidine were supplemented with propofol. The minor surgery reported probably did not include peritoneum incision or abdominal retraction. Vuyk *et al.*[7] reported that the Cp50 of alfentanil during propofol anesthesia was 92 ng/ml for intubation, 55 ng/ml for skin incision, 84 ng/ml for opening of the peritoneum, and 66 ± 38 ng/ml for the intraabdominal part of surgery.[7] Therefore, the ratio of alfentanil Cp50pi to Cp50si for lower abdominal surgery was 1.53. In our study, the ratios of Cp50pi and Cp50ret to Cp50si were 1.33 and 1.50, respectively. The results of the Cp50s in our study show that peritoneum incision and abdominal retraction are clearly more intense stimuli than skin incision. Fentanyl decreased the propofol Cp50s, with 3 ng/ml fentanyl reducing the Cp50s from 56% to 76%.

The effects of the interaction between propofol and fentanyl on hemodynamic response after surgical stimulation were different from the effects on somatic response after skin incision, peritoneum incision, and abdominal retraction. The sBP increases after surgical stimulation were suppressed significantly by fentanyl (table 1 and figs. 5B, 6B, and 7B). When sufficient suppression of hemodynamic response after surgical stimulation is considered as less than a 30% sBP increase, the hemodynamic response after skin incision is adequately suppressed if enough propofol or fentanyl for suppression of somatic response is administered. However, less than 3 ng/ml fentanyl is not adequate to control hemodynamic response after peritoneum incision or abdominal retraction, even when sufficient propofol to suppress somatic response is administered.

Propofol has sedative and hypnotic effects, whereas fentanyl acts mainly as an analgesic agent, producing poor sedation, even at high concentrations. Consequently, in combination, fentanyl and propofol supplement one another and provide satisfactory anesthetic conditions to various noxious stimuli.[3,9]

Billard *et al.*[16] found that increasing propofol did not modify the hemodynamic response to intubation. When associated with propofol, fentanyl decreased the amplitude of the blood pressure response to various noxious stimuli.[9,18] In our study, the depth of anesthesia provided by propofol is not the main factor in the suppression of hemodynamic response to skin incision, peritoneum incision, and abdominal retraction. Somatic-response suppression correlated mainly with fentanyl for skin incision, with propofol and fentanyl both for peritoneum incision, and with propofol for abdominal retraction (table 4). Propofol significantly decreased sBP in a concentration-dependent manner, and fentanyl had no significant effect on sBP when surgical stimulation did not exist (fig. 2, table 1). When surgical stimulation existed, fentanyl significantly suppressed increases in sBP after stimulation, and propofol had no significant effect on such increases (table 1, figs. 5, 6, and 7).

Fentanyl plasma concentrations of 1 or 2 ng/ml provide analgesia,[19] but levels of at least 2 to 3 ng/ml usually are necessary during surgery if the only inhaled agent is nitrous oxide. In our study, we found that fentanyl requirements during surgery depend on the kind of stimulation. When somatic response is controlled, less than 3 ng/ml fentanyl will be sufficient to control hemodynamic response after skin incision. However, more than 3 ng/ml fentanyl will be necessary after peritoneum incision or abdominal retraction, even when somatic response is controlled. In a study of unpremedicated patients anesthetized with a fentanyl infusion and 70% nitrous oxide in oxygen, the concentration of fentanyl necessary to prevent an autonomic response to skin incision was 4.17 ng/ml.[2] The reported fentanyl concentrations for suppression of hemodynamic response with nitrous oxide generally correspond with the fentanyl concentration combined with propofol in our study.

Our study clearly shows that propofol reduces intraoperative analgesic requirements for somatic response and that a synergistic effect of propofol on hemodynamic response exists in the three kinds of surgical stimulation studied. A previous study of propofol suggested that propofol had no analgesic effects.[20] However, subsequent studies have suggested that propofol possesses analgesic properties.[21–23] Some studies suggest that subhypnotic doses of propofol (0.25 − 0.5 mg/kg) reduce the sensitivity to somatic pain[22] and decrease the acute pain evoked by argon laser stimulation.[23] However, if we define pain as the subjective conscious perception of nociception, it remains uncertain whether propofol has analgesic effects.

For the stimulus of abdominal wall retraction, few studies have investigated the pharmacologic property of the stimulus. In the current study, Cp50ret was obtained while the abdominal cavity was widened to maximal exposure by a retractor. There was a synergistic interaction between propofol and fentanyl between somatic and hemodynamic responses after surgical stimulations. However, the somatic response correlated mainly with the propofol concentration, and the hemodynamic response correlated mainly with the fentanyl concentration in all types of stimulation. These results suggest that pain may not be the main factor for somatic response after abdominal wall retraction.

The prevention of a hyperhemodynamic state in response to surgical stimulation is a basic concern with clinical anesthesia and is of obvious interest to all clinicians. Empirically, many patients show a marked increase in blood pressure during the early phase of abdominal surgery, even those who are administered a sufficient anesthetic dose for skin incision. When specific somatic and hemodynamic responses for surgical stimulations are considered at once, more fentanyl will be necessary for peritoneum incision than for skin incision, and more propofol and fentanyl will be necessary for abdominal wall retraction.

In conclusion, this study quantified somatic and hemodynamic reactions to skin incision, peritoneum incision, and abdominal wall retraction. Peritoneum incision and abdominal retraction stimuli were 1.33 to 1.50 times more intense than skin incision. Somatic responses were different than hemodynamic responses. Sufficient concentrations to prevent the somatic responses to skin incision are not always sufficient to attenuate the hemodynamic reaction after peritoneum incision and abdominal retraction, especially less than 3 ng/ml fentanyl. Although skin incision still can be used to represent all noxious stimuli in nonabdominal surgery, anesthesia requirements for stimuli that are more intense than skin incision should be considered during abdominal surgery.

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