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Reduction by Fentanyl of the CP_{50} Values of Propofol and Hemodynamic Responses to Various Noxious Stimuli

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Background: **Propofol and fentanyl infusion rates should be varied according to the patient's responsiveness to stimulation to maintain satisfactory anesthetic and operative conditions. However, somatic and autonomic responses to various noxious stimuli have not been investigated systematically for intravenous propofol and fentanyl anesthesia.**

Methods: **Propofol and fentanyl were administered *via* computer-assisted continuous infusion to provide stable concentrations and to allow equilibration between plasma–blood and effect–site concentrations. The propofol concentrations needed to suppress eye opening to verbal command and motor responses after 50-Hz electric tetanic stimulation, laryngoscopy, tracheal intubation, and skin incision in 50% or 95% of patients (Cp_{50} and Cp_{95}) were determined at fentanyl concentrations of 0.0, 1.0, 2.0, 3.0, and 4.0 ng/ml in 133 patients undergoing lower abdominal surgery. The ability of propofol with fentanyl to suppress hemodynamic reactions in response to various noxious stimuli also was evaluated by measuring arterial blood pressure and heart rate before and after stimulation.**

Results: **The various Cp_{50} values for propofol alone (no fentanyl) for the various stimuli increased in the following order: $Cp_{50\text{loss of consciousness}}$, 4.4 μg/ml (range, 3.8–5.0); $Cp_{50\text{tetanus}}$, 9.3 μg/ml (range, 8.3–10.4); $Cp_{50\text{laryngoscopy}}$, 9.8 μg/ml (range, 8.9–10.8); $Cp_{50\text{skin incision}}$, 10.0 μg/ml (range, 8.1–12.2); and $Cp_{50\text{intubation}}$, 17.4 μg/ml (range, 15.1–20.1; 95% confidence interval). The reduction of $Cp_{50\text{loss of consciousness}}$ with fentanyl was minimal; 11% at 1 ng/ml of fentanyl and 17% at 3 ng/ml of fentanyl. A plasma fentanyl concentration of 1 ng/ml (3 ng/ml) resulted in a 31–34% (50–55%) reduction of the propofol Cp_{50}s for tetanus, laryngoscopy, intubation, and skin incision. Propofol alone depresses prestimulation blood pressure but had no influence on the magnitude blood pressure or heart rate increase to stimulation. Propofol used with fentanyl attenuated the systolic blood pressure increases to various noxious stimuli in a dose-dependent fashion.**

Conclusions: **The authors successfully defined the propofol concentration required for various stimuli. Tracheal intubation was the strongest stimulus. The absence of somatic reactions for propofol does not guarantee hemodynamic stability without fentanyl. Propofol with fentanyl was able to suppress motor and hemodynamic reactions to various noxious stimuli. (Key words: Anesthetics, intravenous: fentanyl; propofol. Anesthetic techniques: tetanic stimulation; tracheal intubation. Anesthetic potency: hemodynamics; motor reaction.)**

THE reduction by fentanyl of the $Cp_{50\text{loss of consciousness}}$ (the propofol blood concentration at which 50% of patients did not respond to verbal command) is much less than its reduction of the propofol $Cp_{50\text{skin incision}}$ (the propofol blood concentration at which 50% of patients did not respond to skin incision).[1] These data suggest that different stimuli require different propofol-fentanyl concentrations to suppress undesirable responses. Propofol and fentanyl infusion rates should be varied according to the patient's responsiveness to stimulation to maintain satisfactory anesthetic and operative conditions and provide rapid recovery of consciousness. The propofol blood concentrations at which 50% and 95% of patients did not respond to verbal command or to skin incision have been previously determined,[1] although the responses to various stimuli such as verbal command, tetanic electrical stimulation, laryngoscopy without intubation, intubation, and skin incision have not been investigated systematically for intravenous propofol and fentanyl anesthesia. One aim of this study was to investigate the reductions by fentanyl on the Cp_{50} of propofol (propofol plasma concentration that results in a 50% probability of no response) and Cp_{95} (propofol plasma concentration that results in a 95% probability of no

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response) for noxious stimulation when both drugs have reached steady biophase concentration.

The lack of motor response is not an accurate predictor of the ability of an agent to depress hemodynamic reaction during isoflurane anesthesia.[2] Blood pressure and heart rate may increase considerably even at end-tidal isoflurane concentrations greater than those needed to obtund motor reaction in patients exposed to noxious stimuli.[2] For example, in patients with coronary heart disease, such hemodynamic responses may be dangerous. The second objective of this study was to examine the relationship between the blood concentration of propofol with fentanyl and its clinical effects on somatic and hemodynamic reactions after various noxious stimuli. This knowledge is required to design an optimal dosage regimen of propofol in total intravenous anesthesia (TIVA).

Propofol and fentanyl were infused by means of a pharmacokinetic model-driven device that is now used to deliver and maintain constant target blood concentrations of propofol.

Materials and Methods

Written informed consent was obtained from each patient after explanation of the study, which was approved by the District Ethics Committee of the Hamamatsu University Hospital. Nonpremedicated patients, aged 20–55 years, American Society of Anesthesiologists' (ASA) physical status of 1 or 2, and scheduled for elective lower abdominal surgery were selected for the study. Exclusion criteria were a history of cardiac, pulmonary, liver, or renal disease, history of esophageal reflux or hiatal hernia, drug or alcohol abuse, opioid medication, or significant obesity (body mass index $>$ 30). On arrival of the patient in the operating room, a cannula used solely for infusions of propofol and fentanyl was inserted into a peripheral vein during local anesthesia. An arterial catheter was inserted in the contralateral arm for sampling of blood.

Patients were randomly allocated to receive fentanyl concentrations of 0.0, 1.0, 2.0, 3.0, or 4.0 ng/ml and then randomly allocated into two sub-groups: low (1.0, 2.0, 3.0, 4.0, 6.0, 9.0 μg/ml) and high (12.0, 14.0, 16.0, 18.0, 22.0, 24.0, 26.0 μg/ml) concentrations of propofol (table 1). Propofol was administered by computer-assisted continuous infusion pumps (CACI), using three-compartmental model with central elimination. The rate of drug-mass change in three compartments can be expressed as three simultaneous differential equations. We solved these equations using published pharmacokinetic microconstants[3] numerically by Runge-Kutta method at the recursive period of 12 s. If the target concentration was set, the computer (NEC 9821, NEC Corp., Tokyo, Japan) tried to find the appropriate infusion rate required to attain the target concentration, if keeping that rate in future step, and computer commanded the infusion pump to keep this rate. We programmed this control software ourselves in the Turbo Pascal language (Borland International, Scotts Valley, CA).

In the preliminary study to test the ability of the pharmacokinetic model to follow changes to dosage rates, stepwise increases with 20-min interval to the target concentrations were introduced after induction of anesthesia in 12 patients (ASA physical status 1). The mean age, height, and weight (35.5 $\pm$ 11.9 yr; 158.7 $\pm$ 8.1 cm; 59.0 $\pm$ 10.3 kg) were almost similar to those of the patients of the main study. The correlation coefficient between measured and predicted blood propofol concentration was 0.84 in the preliminary study, and the general tendency for the measured values to exceed the predicted blood concentration was apparent ($y = 1.67+0.6$; fig. 1). We used corrected propofol concentration with the linear regression in this study to make prediction more applicable in clinical use. Using such a device, it is possible to select a desired target blood concentration and to alter it thereafter if necessary. We used two pumps (ATOM Model 1235, Tokyo, Japan) simultaneously for propofol infusion because the maximum infusion rate of one pump was 200 ml/h in the maintenance mode. The pharmacokinetic variables used in CACI for fentanyl were those previously reported by McClain and Hug.[4]

To ensure equilibration between plasma and effect compartment, CACI for one of the concentrations of fentanyl was started 20 min before propofol administration, and the concentration set by CACI was unchanged until skin incision. Prediction error and the absolute prediction error were calculated for each measured sample. After a 20-min equilibration period for fentanyl, a predicted propofol concentration of 1.0 μg/ml in low dose sub-groups or 12.0 μg/ml in high dose sub-groups was randomly chosen. After a 10-min equilibration period of propofol blood concentration set by CACI, a defined series of stimuli was tested: verbal command, tetanic stimulation of the forearm muscles, laryngoscopy performed to the point at which the vocal cords could be inspected, and laryngoscopy plus intubation.

Table 1. Demographic Data for Each Group

Group	Predicted Fentanyl Concentration (ng/ml)	Predicted Propofol Concentration (μg/ml)	Gender		Age (yr)	Height (cm)	Body Weight (kg)
			Male (n)	Female (n)			
1a	0.0	1.0, 2.0, 3.0, 4.0, 6.0, 9.0	7	9	36.8 ± 12.4 (21–51)	160.3 ± 11.6	55.1 ± 13.2
1b	0.0	12.0, 14.0, 16.0, 18.0, 22.0, 24.0, 26.0	7	8	35.8 ± 10.5 (24–48)	152.4 ± 8.9	60.2 ± 10.8
2a	1.0	1.0, 2.0, 3.0, 4.0, 6.0, 9.0	6	9	37.5 ± 16.5 (23–50)	165.7 ± 10.4	61.0 ± 11.0
2b	1.0	12.0, 14.0, 16.0, 18.0, 22.0	5	9	38.2 ± 13.8 (25–52)	157.5 ± 11.5	59.2 ± 8.5
3a	2.0	1.0, 2.0, 3.0, 4.0, 6.0, 9.0	6	7	41.8 ± 14.8 (24–50)	155.4 ± 7.2	58.0 ± 11.8
3b	2.0	12.0, 14.0, 16.0, 18.0, 22.0	6	8	37.5 ± 15.1 (25–51)	161.4 ± 8.6	61.3 ± 9.8
4a	3.0	1.0, 2.0, 3.0, 4.0, 6.0, 9.0	5	7	39.0 ± 13.2 (23–49)	165.5 ± 7.9	60.5 ± 10.1
4b	3.0	12.0, 14.0, 16.0, 18.0, 22.0	4	7	38.8 ± 14.4 (22–49)	152.9 ± 8.5	62.0 ± 11.2
5a	4.0	1.0, 2.0, 3.0, 4.0, 6.0, 9.0	5	7	36.6 ± 11.6 (20–48)	162.0 ± 7.6	59.6 ± 11.0
5b	4.0	12.0, 14.0, 16.0, 18.0, 22.0	6	5	39.6 ± 15.2 (23–49)	160.1 ± 10.4	56.8 ± 9.8

Values are mean ± SD (range).

Each patient of low-dose subgroups was tested at each propofol concentration in the order of 1.0, 2.0, 3.0, 4.0, 6.0, and 9.0 μg/ml (table 1). Each series of stimuli was performed after 10-min equilibration period after each change in propofol concentration. Every stimulation was performed after the motor and the hemodynamic reactions caused by the previous stimulation had returned to the prestimulation conditions. It took 1 min after verbal command, 3 min after tetanus, 3 min after laryngoscopy, and 3–5 min after intubation. Every kind of stimulation should be tested at all concentrations of propofol, whereas in present study, for practical and ethical reasons, tetanus and laryngoscopy were tested after the response to verbal command turned to negative, and intubation was performed only after responses to tetanus and laryngoscopy were negative. When the response to stimulation was positive, the next series of stimuli was tested at the higher concentration of propofol. The measurement took less than 150 min (six times less than 25 min) for each patient: 3 min for increasing blood propofol concentration; 10 min for equilibration between blood and effect-site; and less than 12 min for measurements in each propofol concentration. When the response to intubation was positive at 9.0 μg/ml of propofol in the low-dose group, the trachea was intubated after administration of 1 mg/kg of succinylcholine. Each patient of high-dose subgroups was tested in the same manner as the low-dose subgroups, but there were no patients in whom succinylcholine was required.

As for verbal command, the patients were asked to open their eyes or to otherwise indicate if they were still conscious. If no response to these stimuli occurred, the patients were stimulated by gently rubbing their shoulders, and the response was noted. Plasma concentration to provoke loss of consciousness ($Cp_{loss\ of\ consciousness}$) was defined as unresponsiveness to verbal and tactile stimuli.

As for tetanic stimulation, two disposable electrodes were placed on the ulnar side of forearm, which was stimulated with 10-s bursts of 50-Hz, 80-mA electric current from a nerve stimulator (NS252 Peripheral Nerve Stimulator, Fisher & Paykel Healthcare, Auckland, New Zealand). When using surface electrodes, constant current is the most effective way to achieve consistent nerve stimulation. The voltage necessary to deliver the constant current should vary automatically with changing impedance, and the stimulating current pulse

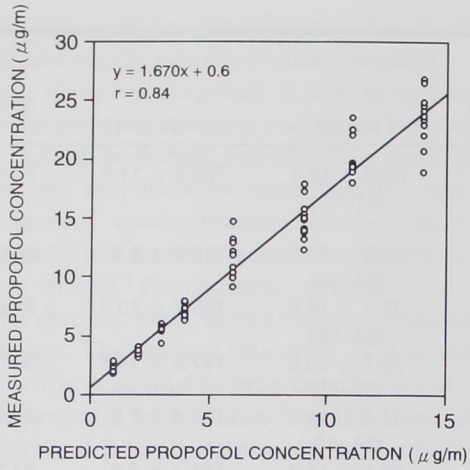

Fig. 1. Predicted *versus* measured propofol concentrations in 12 patients of preliminary study, as obtained with pharmacokinetic parameter set of Gepts *et al.*[3] r = correlation coefficient.

should be of sufficient intensity to achieve consistent stimulation. The nerve stimulator used in the present study delivers a constant current stimulation pulse. The response and plasma concentration for tetanic stimulation ($Cp_{tetanus}$) was noted and classified as positive if the patient showed a gross purposeful movement. Swallowing and slight movement of the shoulder or arm of the stimulated side were not classified as positive responses.

Laryngoscopy was performed for 10 s when the vocal cords could be inspected. The response and plasma concentration for laryngoscopy ($Cp_{laryngoscopy}$) was defined when a gross purposeful movement was noted. The response and plasma concentration for intubation ($Cp_{intubation}$) was evaluated in two phases. First, the adequacy of conditions for laryngoscopy was observed. Such conditions were defined as: (1) easy visualization of the glottis; (2) relaxation of the vocal cords; and (3) absence of extremity movement. Second, the incidence of coughing, or "bucking," immediately after an otherwise successful intubation was recorded. After the defined series of stimuli, skin incision was tested only once at the randomized target propofol concentrations of 3.0, 4.0, 6.0, 9.0, 12.0, 14.0, and 16.0 μg/ml at each fentanyl concentration to define the response and plasma concentration ($Cp_{skin\ incision}$).

The ability of propofol with fentanyl to suppress hemodynamic reactions (arterial blood pressure and heart rate) in response to noxious stimuli was evaluated by measuring arterial blood pressure and heart rate before and after stimulation. The mean systolic blood pressure and heart rate values during 1 min before stimulation were recorded and used as the prestimulation values. The maximum value during 3 min after stimulation was taken for the poststimulation value. Systolic blood pressure and heart rate values of all patients were correlated to the propofol concentrations with respective different fentanyl concentrations using linear regression. The hemodynamic response to stimulation was defined for each patient as the percent change of prestimulation value on systolic blood pressure. The numeric values at each stimulation pattern were obtained by taking the average blood pressure (or heart rate) increase at the Cp_{50} and the Cp_{95} values of each stimulation calculated by using linear regression.

Arterial blood samples for analysis of the plasma propofol concentration were taken at 0 min and 6 min after 10-min equilibration of propofol infusion. Blood samples were kept on ice and stored at 5°C until extraction and assay. Plasma concentrations of propofol were determined using high-performance liquid chromatography with fluorescence detection at 310 nm and after excitation at 276 nm (CTO-10A and RF550, Shimadsu, Kyoto, Japan).[5] The areas under the chromatographic peaks were calculated with an integrator (C-R7A, Shimadsu, Kyoto, Japan). For each batch of blood samples (from one patient), a separated standard curve was computed by adding pure propofol liquid to drug-free human plasma to make up concentrations of 1.0, 5.0, 10.0, and 25.0 μg/ml. Linear regression (method of least squares) was used with serum propofol concentration as the dependent variable. Propofol concentrations in this study were calculated by using the obtained regression equation. The lower limit of detection was 19 ng/ml, and the coefficient of variation was 8.2%.

Arterial blood samples for fentanyl concentration were taken at 20 min and 90 min after the start of fentanyl infusion. The blood samples were immediately placed on ice, after which the plasma was separated and frozen at −70°C until assayed. The plasma concentration of fentanyl was measured by gas chromatograph-mass spectrometer (Hewlet Packard, Model 5989, CA) in an outside laboratory. The lower limit of detection was 0.2 ng/ml.

Electrocardiogram, intraarterial blood pressure, heart rate, end-tidal carbon dioxide, oxyhemoglobin saturation (Sp_{O2}), and body temperature were monitored continuously throughout the study. Spontaneous respiration was manually assisted when necessary. If hypotension (less than 80 mmHg in systolic arterial pressure)

occurred even after stimulation, the patient's blood pressure was restored by a combination of fluid administration and ephedrine.

The responses of patients to stimulation at each concentration were subjected to probit analysis to determine values for Cp_{50} and Cp_{95} and the 95% confidence limits (SPSS advanced Statistics 6.1 version). An analysis of variance and Fisher's test were used to check for the somatic and hemodynamic effects (the increases of systolic blood pressure or heart rate after stimulation at Cp_{50} and Cp_{95}) of various stimulation patterns. A significance level of $P < 0.05$ was applied for all tests. Multiple regression was used to evaluate the influence on the absolute increase of blood pressure or heart rate in various stimulation by the following parameters: the positive motor reaction to stimulation, plasma fentanyl concentration, and plasma propofol concentration. The occurrence of a motor reaction was expressed with 1 for positive and 0 for absence of reaction.

Results

The responses to the defined stimuli of verbal command, tetanic stimulation, laryngoscopy, intubation, and skin incision were evaluated in 133 patients. One patient of Group 2, two patients of Group 3, five patients of Group 4, and five patients of Group 5 had bradycardia (< 50 beats/min) after the fentanyl infusion. In each case, intravenous atropine, 0.25 mg, restored the heart rate to the preinduction value. Twelve patients required intravenous ephedrine (4–8 mg) because of hypotension associated with the larger doses of propofol that were excluded from the analysis of measurement. No significant difference was found among the groups concerning age, sex ratio, weight, and height (table 1). Blood gases and hemoglobin concentrations did not change significantly; rectal temperature decreased slightly from 36.4 ± 0.6°C at the beginning to 36.0 ± 0.8°C at the end of the measurement period. In no case did recall of awareness of the tetanic stimulation, laryngoscopy, and intubation occur when patients were questioned 24 h postoperatively.

The measured plasma propofol concentration *versus* time profiles for different target concentrations are shown in figures 2A and 2B. The mean and absolute prediction errors for CACI administration of propofol were −4.1% and 20.2%, respectively. The measured plasma fentanyl concentration *versus* time profiles for Group 2 (target concentration, 1 ng/ml), Group 3 (2 ng/ml), Group 4 (3 ng/ml), and Group 5 (4 ng/ml) are shown in figure 3. The mean and absolute prediction errors for CACI administration of fentanyl were 33.4% and 41.3%, respectively.

Laryngoscopy was tried after the response for verbal command was negative. Visualization of the vocal cords by standard laryngoscopy often was possible after propofol infusion. Pharyngeal and laryngeal reactivity were similarly depressed. Widely abducted, immobile vocal cords were frequently observed during laryngoscopy. Intubation was tried only after negative responses to tetanus and laryngoscopy to avoid excessive reactions. Although there were some patients in whom slight laryngospasm occurred after extubation when the response to intubation was positive, the reaction disappeared rapidly at the next higher target concentration of propofol, and there was no need to manage laryngospasm with other drugs.

The responses to various specific stimuli at the different concentrations of propofol and fentanyl are summarized in table 2. The Cp_{50}s of verbal command, tetanus, laryngoscopy, intubation, and skin incision in Group 1 (propofol alone) were 4.4, 9.3, 9.8, 17.4, and 10.0 μg/ml, respectively. The reduction of Cp_{50} propofol of verbal command by fentanyl was minimal (table 2). The reduction of Cp_{50} of propofol by fentanyl was evident, which suggests a possible dynamic interaction between propofol and fentanyl. According to this model, a plasma fentanyl concentration of 1 ng/ml resulted in a 11%, 34%, 31%, 32%, and 32% reduction of the propofol Cp_{50}s for verbal command, tetanus, laryngoscopy, intubation, and skin incision, respectively. Increasing the plasma fentanyl concentration to 3 ng/ml resulted in a 17%, 51%, 50%, 51%, and 55% reduction of the propofol Cp_{50}s for verbal command, tetanus, laryngoscopy, intubation, and skin incision, respectively. Increasing the fentanyl concentration beyond 3 ng/ml produced a smaller reduction in Cp_{50}s for various noxious stimuli, demonstrating a ceiling effect. There were significant differences between the Cp_{50}s for various stimuli: intubation *versus* verbal command, tetanus, laryngoscopy, and skin incision and verbal command *versus* tetanus, laryngoscopy, and skin incision. There also were significant differences between the Cp_{95}s: intubation *versus* verbal command, tetanus, laryngoscopy, and skin incision and verbal command *versus* tetanus, laryngoscopy, and skin incision. The Cp_{50} values increased in the order of verbal command < tetanic stimulation = laryngoscopy = skin incision < intubation. According to $Cp_{50}/Cp_{50\text{skin incision}}$ shown in table 2, response to te-

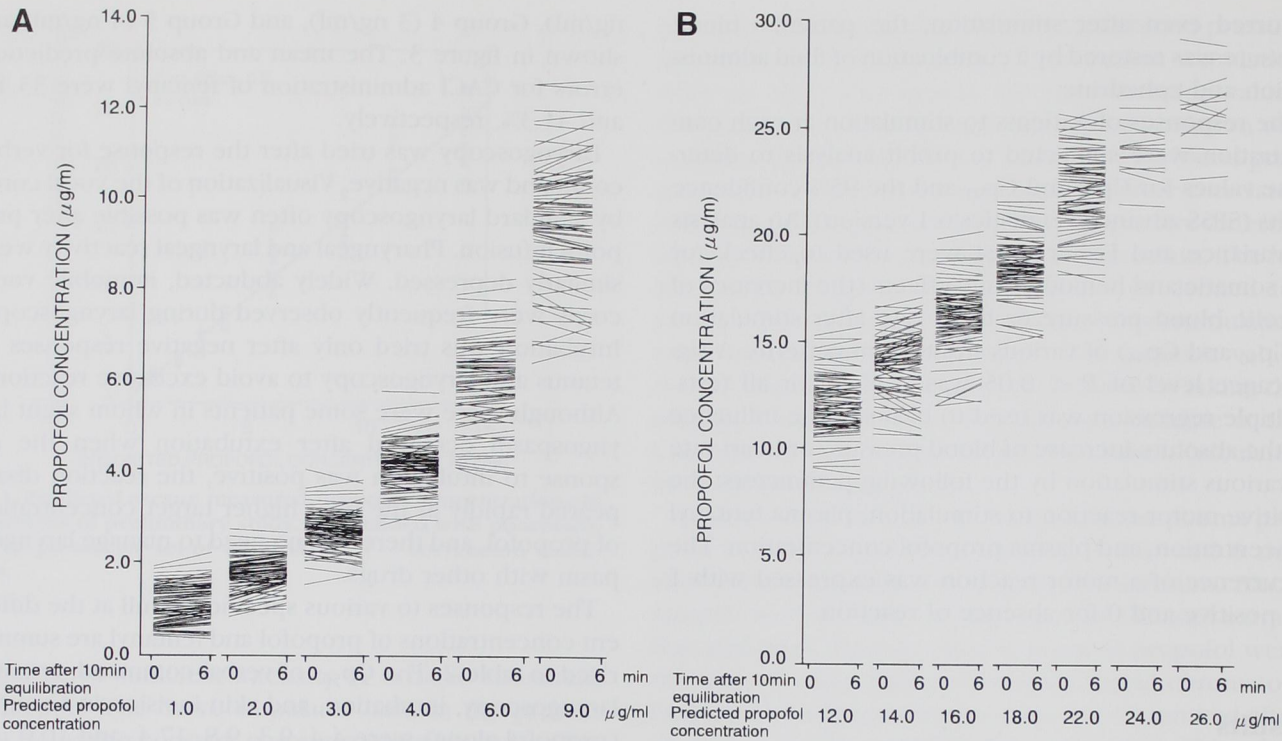

Fig. 2. The mean measured, constant plasma propofol concentration *versus* time profiles for different target levels in (*A*) low- or (*B*) high-dose subgroups of propofol. Each propofol concentration was stable during measurements.

tanic stimulation and laryngoscopy was similar to skin incision, even if propofol was used with fentanyl.

The systolic blood pressure and heart rate values in various noxious stimuli are given in figure 4A (tetanus), figure 4B (laryngoscopy), figure 4C (intubation), and figure 4D (skin incision). Solid lines show concentration-response regressions and 95% confidence intervals for systolic blood pressure and heart rate before stimulation; dotted lines indicate those after stimulation. The increases of the average systolic blood pressure and heart rate at the corresponding Cp_{50} and Cp_{95} values of each stimulation were calculated with linear regression. A statistically significant increase for systolic blood pressures at Cp_{50} and Cp_{95} of the motor reaction existed among tetanus, laryngoscopy, intubation, and skin incision in Groups 1, 2, and 3 (table 3). In Group 1 (fentanyl = 0 ng/ml), the regression line drawn through the prestimulation values was virtually parallel to the line drawn through the poststimulation values of tetanus, laryngoscopy, intubation, and skin incision (figs. 4A-D). This has shown that the absence of somatic reactions does not guarantee hemodynamic stability without fentanyl. In the other groups in which fentanyl was infused simultaneously with propofol, the systolic blood pressure increases to various noxious stimuli were attenuated in a dose-dependent fashion of propofol. The response of systolic blood pressure increased in the order of tetanic stimulation < laryngoscopy < skin incision < intubation. Heart rates at Cp_{50} and Cp_{95} of the motor reaction were not influenced significantly in each group nor in each stimulation except between intubation and tetanus and between skin incision and tetanus in Group 1 and between tetanus and intubation in Group 2 (table 2). Analysis using multiple regression showed that systolic blood pressure response was influenced most by the fentanyl concentration in each stimulation (table 4). The propofol concentration and the concomitantly occurring motor reaction did not influence the hemodynamic response.

Discussion

Regression analysis by stepwise increases of propofol target concentration revealed that the parameter sets we used underpredicted the concentrations, so that the

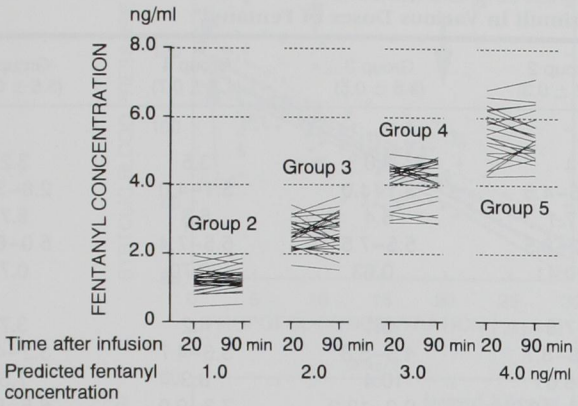

Fig. 3. The measured plasma fentanyl concentration *versus* time profiles for Group 2 (1 ng/ml), Group 3 (2 ng/ml), Group 4 (3 ng/ml), and Group 5 (4 ng/ml).

measured concentrations were higher than predicted concentration (fig. 1). Propofol has been shown to reduce cardiac output and hepatic blood flow.[6] For a drug with a high hepatic extraction ratio (like propofol), this might result in a decreased clearance at higher concentrations and which may contribute to the observed increase in the measured - predicted concentration difference. Concurrently, a reduced cardiac output at the greater concentration would result in slower distribution to peripheral compartments. To control blood concentration optimally, the pharmacokinetic parameter set provided to the computer model should match the pharmacokinetics of the patients. By using linear regression for measured concentration, we corrected the prediction of propofol concentration calculated with Gepts' parameter (fig. 1).[3] It proved adequate with acceptable prediction errors.

There is a lag between changes in the plasma concentration and the corresponding changes in the central nervous system (CNS) because of the blood - CNS equilibration time.[7] Drug concentration at the effect site, not the plasma concentration, governs the drug effect. The stability of a response over a period of time implies stability in the biophase concentration. It is not currently feasible to measure such a concentration directly in the cerebral cortex, where the effects of anesthetics such as propofol are presumed. In this study, blood propofol concentrations predicted by the microcomputer were validated by the measurements of blood propofol concentrations. Equilibration within the central compartment was reliable during measurements because the target propofol concentration was maintained for the preset equilibration 10 min before measurement. The effect site concentration is difficult to measure, but it is assumed to be in equilibrium with the blood or plasma concentration.[4,8-10] A slower equilibration of fentanyl into the effect site, relative to propofol, dampens the increase in opioid concentration at the effect site.[11] But, a 20-min period for fentanyl infusion in this study was enough to ensure equilibration between plasma and effect - site concentration.

Considerable interpatient variability has been reported, and the relationship between infusion rates and measured blood concentrations varies greatly between studies.[1,12,13] In our study, using a microcomputer-controlled infusion system, we endeavored to devise direct approach, relating patient response to predicted and measured blood propofol concentrations.

Smith *et al.*[1] reported that for propofol alone, the $Cp_{50loss\ of\ consciousness}$ was 3.3 μg/ml, and the $Cp_{95loss\ of\ consciousness}$ was 5.4 μg/ml. On the other hand, a propofol blood concentration of 2.5 μg/ml was required for satisfactory hypnosis during surgery.[14] In this study, $Cp_{50loss\ of\ consciousness}$ was 4.4 μg/ml when propofol was administered alone. It is likely that the lower concentration of $Cp_{50loss\ of\ consciousness}$ in previous reports may be a result of a difference in the form of stimulation. In this study, if no response to verbal command occurred, the patients were stimulated by gently rubbing their shoulders, and the response was noted. *Loss of consciousness* was defined as unresponsiveness to verbal and tactile stimuli. The reduction by fentanyl of the propofol $Cp_{50loss\ of\ consciousness}$ was minimal, which corresponds to the report by Smith.[1]

After a 20 - 30 mg temazepam premedication, Davidson[15] reported the venous $Cp_{50skin\ incision}$ of propofol alone as 8.1 μg/ml. The interaction with temazepam and the use of venous blood concentrations probably explain why the value by Davidson is lower than our $Cp_{50skin\ incision}$ value of 10.0 μg/ml. Smith *et al.*[1] reported that the whole-blood propofol concentration for the propofol $Cp_{50skin\ incision}$ was 15.2 μg/ml, which is higher than that of our study. They also reported that the reduction of $Cp_{50skin\ incision}$ by fentanyl was 63% with 1 ng/ml fentanyl and 89% with 3 ng/ml fentanyl. These values are higher than 32% with 1 ng/ml fentanyl and 55% with 3 ng/ml of fentanyl in present study. Although there is no clear explanation for this difference, it may be explained partly by difference of incision site. The skin incision site in our study was restricted to lower abdominal site.

Tetanic stimulation needs a well-defined electrical current and a standardized method of electrode placement.

Table 2. Cp50 and Cp95 for Propofol to Prevent Motor Response to Stimuli in Various Doses of Fentanyl*

Stimulation	Group 1 (0)	Group 2 (1.2 ± 0.3)	Group 3 (2.6 ± 0.5)	Group 4 (4.1 ± 0.7)	Group 5 (5.5 ± 0.8)
Verbal command					
Cp50 (μg/ml)	4.4	4	3.6	3.5	3.2
Cp50 confidence limits (μg/ml)	3.8–5.0	3.5–4.5	3.1–4.0	3.1–4.0	2.8–3.6
Cp95 (μg/ml)	7.8	7.1	6.4	6.3	5.7
Cp95 confidence limits (μg/ml)	6.7–9.3	6.2–8.5	5.5–7.5	5.5–7.4	5.0–6.7
Cp50 verbal command/Cp50 skin incision	0.44	0.41	0.63	0.70	0.76
Tetanus					
Cp50 (μg/ml)	9.3	7.8	5.1	4.2	3.7
Cp50 confidence limits (μg/ml)	8.3–10.4	6.8–8.7	4.5–5.8	3.6–4.7	3.2–4.3
Cp95 (μg/ml)	18.9	15.6	10.4	8.3	7.5
Cp95 confidence limits (μg/ml)	16.7–21.6	13.7–18.0	9.0–12.2	7.3–9.9	6.5–8.9
Cp50 tetanus/Cp50 skin incision	0.93	0.80	0.89	0.84	0.88
Laryngoscopy					
Cp50 (μg/ml)	9.8	10.1	6.3	5.6	4.6
Cp50 confidence limits (μg/ml)	8.9–10.8	9.2–11.1	5.6–7.0	5.0–6.2	4.0–5.1
Cp95 (μg/ml)	16.3	17.1	10.4	9.2	7.4
Cp95 confidence limits (μg/ml)	14.8–18.2	15.5–19.0	9.3–11.9	8.2–10.6	6.6–8.5
Cp50 laryngoscopy/Cp50 skin incision	0.98	1.03	1.11	1.12	1.10
Intubation					
Cp50 (μg/ml)	17.4	16.4	10.6	9.8	7.9
Cp50 confidence limits (μg/ml)	15.1–20.1	14.2–18.8	9.1–12.3	8.3–11.6	6.6–9.3
Cp95 (μg/ml)	34.8	32.6	21.2	19.6	15.7
Cp95 confidence limits (μg/ml)	29.6–42.4	27.8–39.6	18.1–26.6	16.5–23.9	13.2–19.0
Cp50 intubation/Cp50 skin incision	1.74	1.67	1.86	1.96	1.86
Skin incision					
Cp50 (μg/ml)	10.0	9.8	5.7	5.0	4.2
Cp50 confidence limits (μg/ml)	8.1–12.2	7.7–12.2	4.3–7.4	3.7–6.5	3.0–5.5
Cp95 (μg/ml)	17.7	17.4	10.1	8.8	7.4
Cp95 confidence limits (μg/ml)	14.3–24.3	13.9–24.0	7.8–14.5	6.7–12.8	5.5–10.7

*The patients who required atropine or ephedrine because of bradycardia or hypotension were excluded. The values in parentheses for each group indicate the measured fentanyl concentration (ng/ml; mean ± SD).

It has been used in place of skin incision in a nonstandardized fashion,[16–19] but it was never evaluated systematically during propofol administration. Precision depends not only on correct estimation of the physiologic parameters peculiar to the patient but also on the stimulation technique and the measurement of the effect. Saidman and Eger[16] used 1.2-ms pulses of 30–45 V at 50 Hz for a maximum of 1 min applied through two 20-gauge needles inserted through the skin of the forearm. The $MAC_{tetanus}$ obtained for halothane by this method was apparently lower than $MAC_{skin\ incision}$. The $MAC_{tetanus}$ of 10-s bursts of 50 Hz and 50 mA for isoflurane was also lower than $MAC_{skin\ incision}$.[20] Hornbein[17] used 100-Hz square wave pulses of 0.17-ms duration at 80–110 V for 10 s using needle electrodes placed close to the ulnar nerves at both wrists to determine MAC for nitrous oxide. Kopman *et al.*[19] reported that a current of 50 mA was sufficient to cause stimulation. In the present study, there was no significant difference between $Cp_{50tetanus}$ and $Cp_{50skin\ incision}$ in somatic response, but there were significant differences in hemodynamic responses at $Cp_{50tetanus}$ and $Cp_{50skin\ incision}$. Although the advantage of tetanic stimulation is the ease of performance, repeatability, and reproducibility, evaluating the response to tetanic stimulation may be still difficult.

The somatic response to surgical incision has shown Cp_{50} and Cp_{95} values of 1.7 μg/ml and 3.4 μg/ml, respectively, in patients given a constant-rate propofol infusion after morphine premedication and a standardized induction with propofol.[21] The values of $Cp_{50skin\ incision}$ and $Cp_{95skin\ incision}$ with propofol alone were 10.0 (95% confidence interval, 8.1–12.2 μg/ml) and 17.7 μg/ml (95% confidence interval, 14.3–24.3 μg/ml), respectively, in this study. These values are less than those of Cp_{50} of 15.2 μg/ml (95% confidence interval, 7.6–22.8 μg/ml) and Cp_{95} of 27.4 μg/ml reported by Smith *et al.*[1]

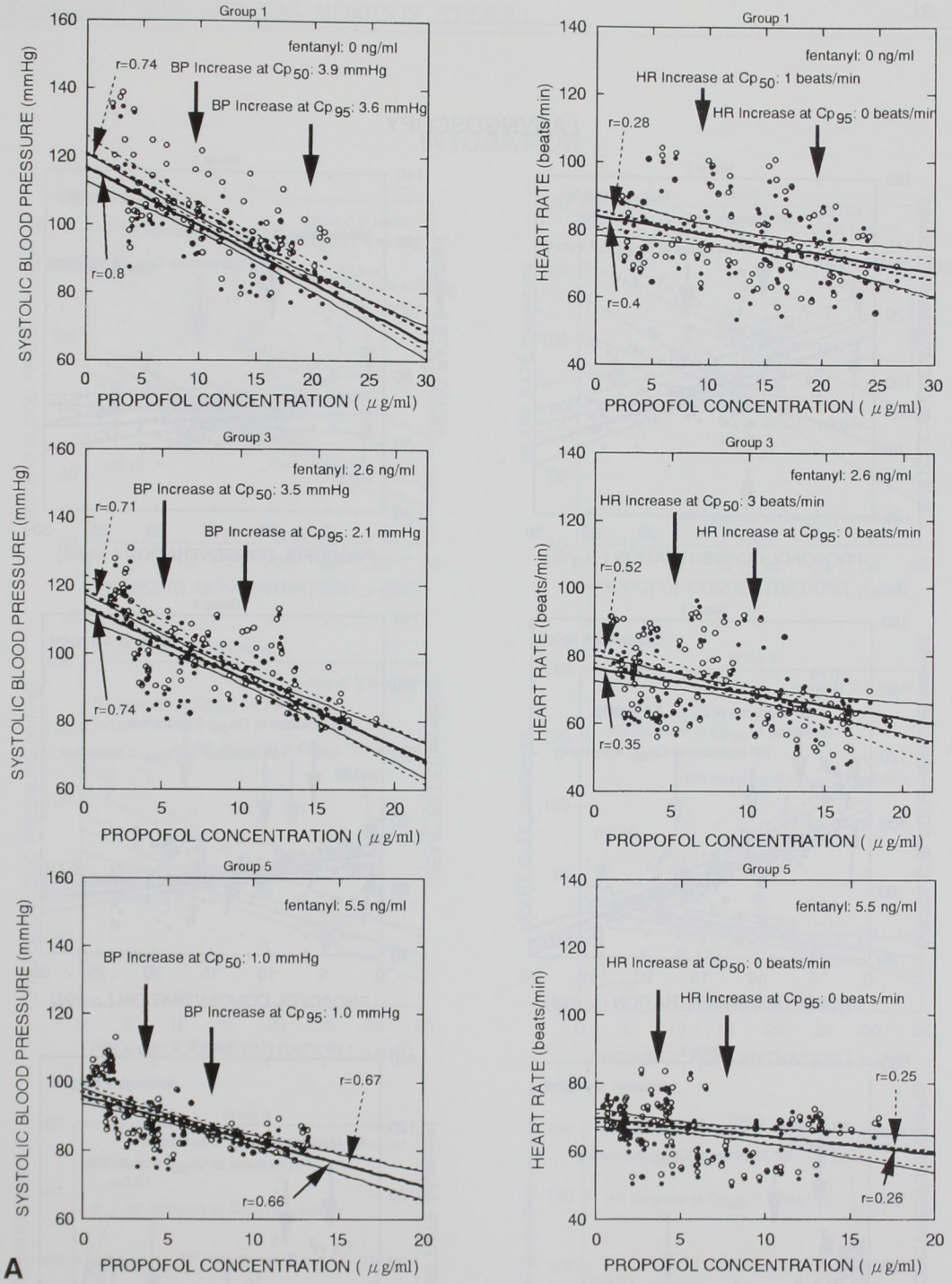

Fig. 4. Responses of systolic blood pressure (mmHg) and heart rate (beats/min) to tetanus (*A*), laryngoscopy (*B*), intubation (*C*), and skin incision (*D*). *Filled circles* are systolic blood pressure and heart rate values before stimulation; *open circles* are systolic blood pressure and heart rate values after stimulation. *Solid lines* show concentration–response regressions and 95% confidence intervals for systolic blood pressure and heart rate before stimulation; *dotted lines* indicate those after stimulation. The correlation coefficient r to these lines is indicated in the figures. Vertical arrow = Cp_{50}s and Cp_{95}s of propofol for motor response to the various stimuli.

We measured Cp_{50} and Cp_{95} in the patients for elective lower abdominal surgery, and the 95% confidence intervals were smaller than those reported by Smith *et al.*[1]

Skin incision has been used as a standard stimulus in most concentration *versus* response relationship studies for anesthetics.[22] However, it has the disadvantages

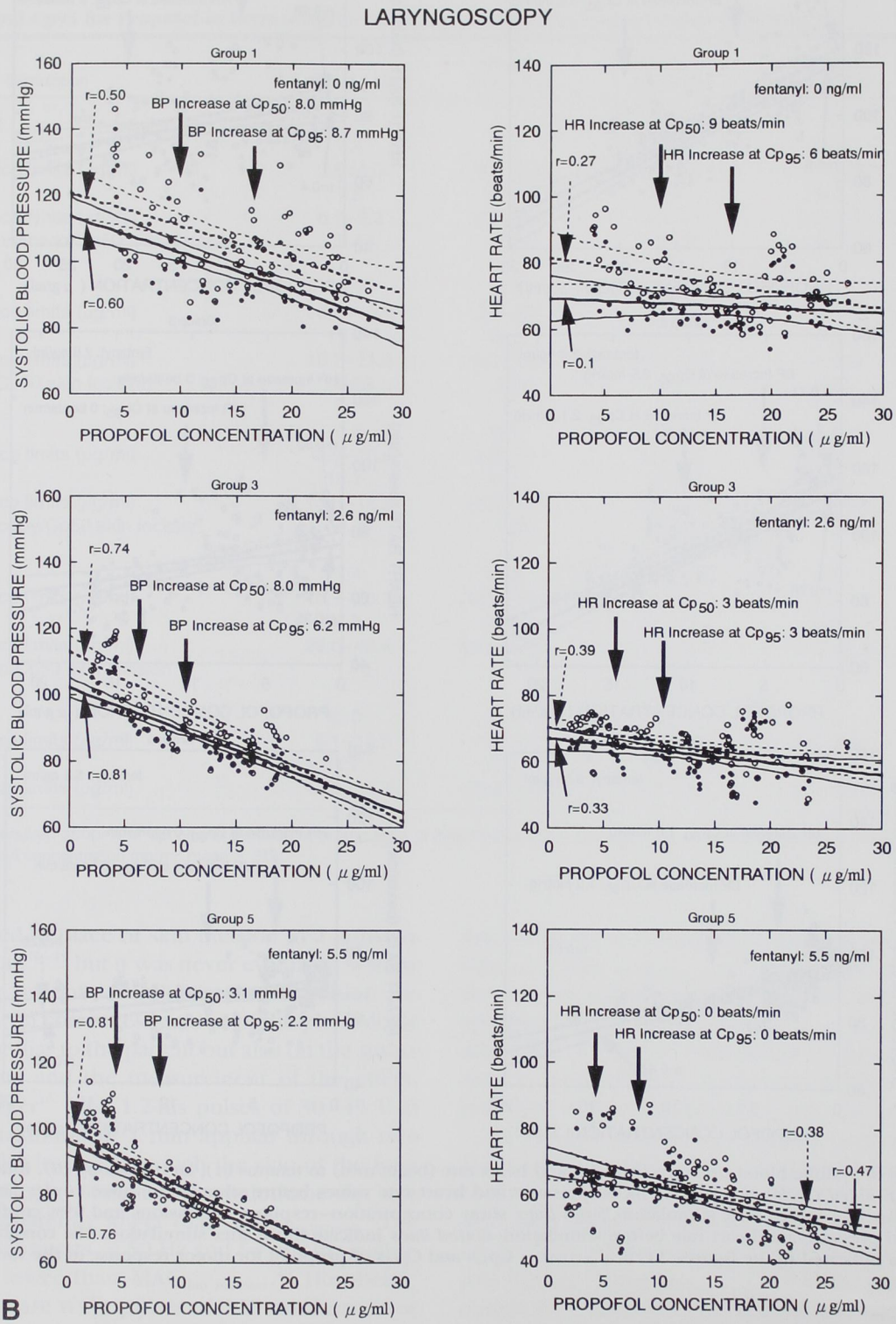

Fig. 4. ***continued***

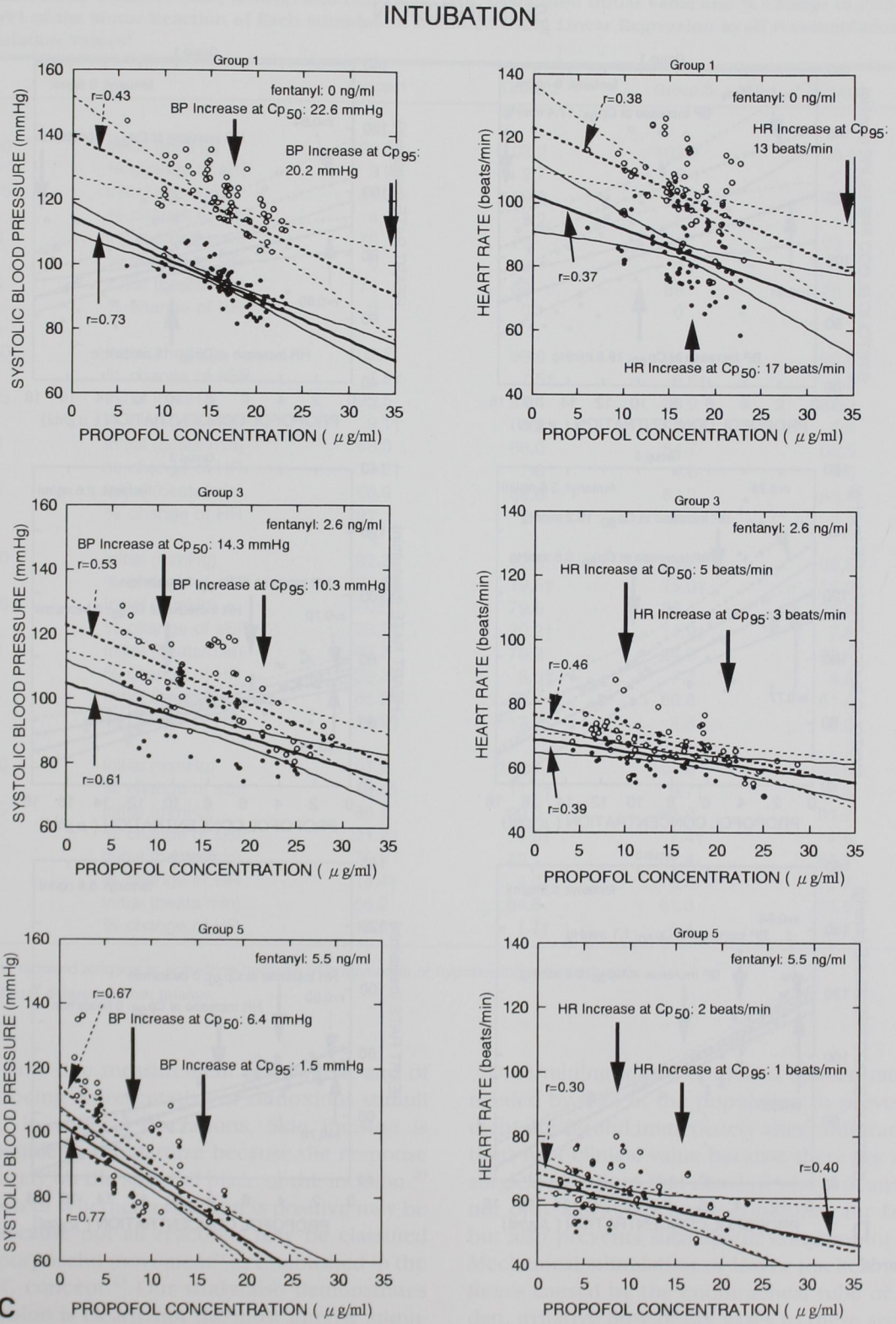

Fig. 4. ***continued***

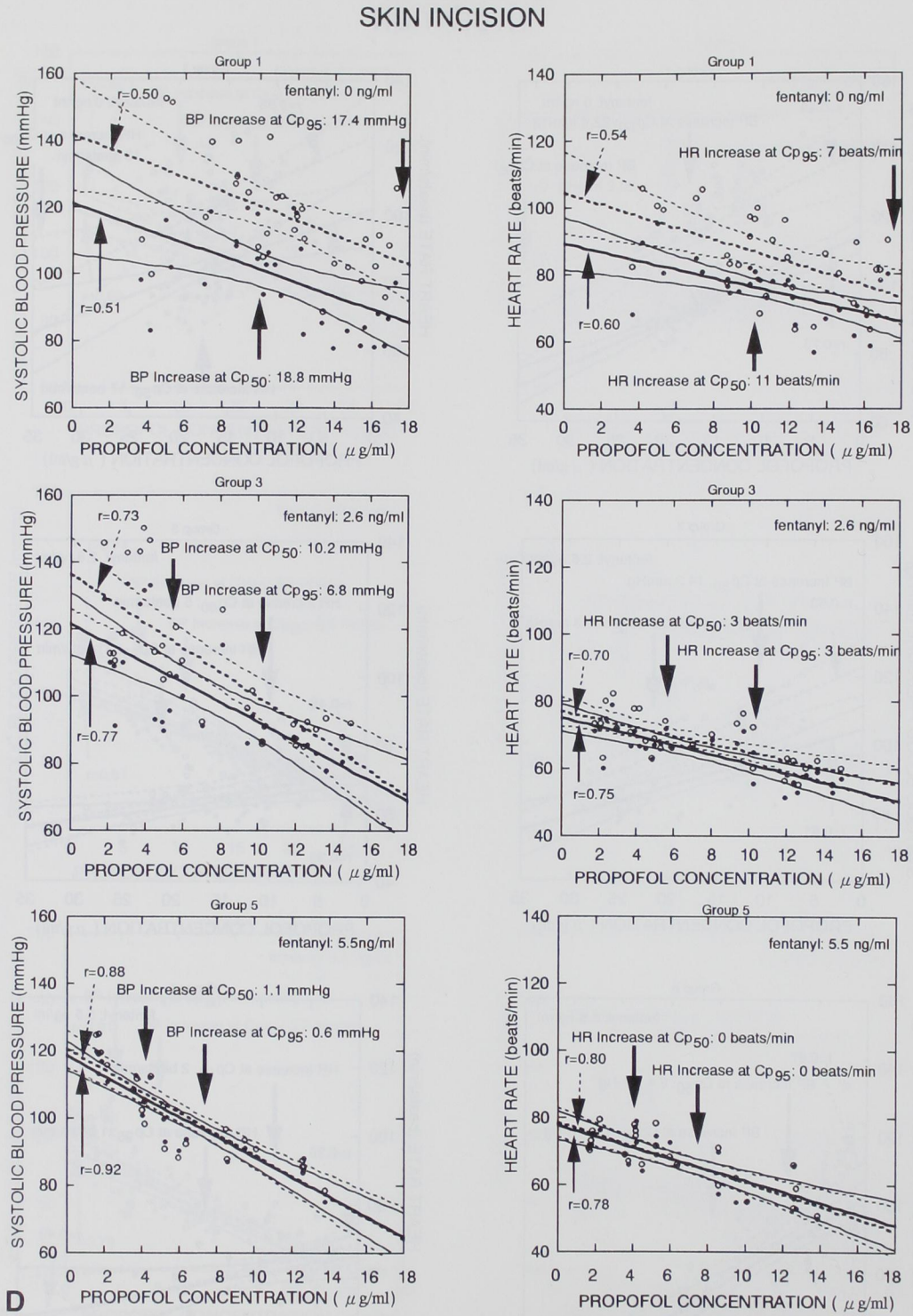

Fig. 4. ***continued***

Table 3. Systolic Blood Pressure (sBP, mmHg) and Heart Rate (HR, beats/min; Initial Value and % Change to Prestimulation) at Cp50 and Cp95 of the Motor Reaction of Each Stimulation Obtained Using Linear Regression to all Prestimulation Values and the Poststimulation Values*

		Group 1	Group 2	Group 3	Group 4	Group 5
Tetanus						
sBP at Cp50	Initial (mmHg)	100.7	102.2	103.2	96.1	91.1
	% change of sBP	3.9	2.7	3.4	2.8	1.1
sBP at Cp95	Initial (mmHg)	84.3	89.6	92.3	89.8	86.1
	% change of sBP	4.3	3.2	2.3	1.7	0.9
HR at Cp50	Initial (beats/min)	79	75	73	70	68
	% change of HR	0	3	4	3	0
HR at Cp95	Initial (beats/min)	74	69	69	70	66
	% change of HR	0	0	0	0	0
Laryngoscopy						
sBP at Cp50	Initial (mmHg)	102.7	99.6	94.0	92.9	89.8
	% change of sBP	7.8†	7.5†	8.5†	6.9	3.5
sBP at Cp95	Initial (mmHg)	95.5	91.4	88.9	88.0	85.3
	% change of sBP	9.1†	8.2†	7.0†	8.9	1.2
HR at Cp50	Initial (beats/min)	68.0	66.0	64.7	65.5	66.9
	% change of HR	13.2†	7.6	4.6	4.6	0.0
HR at Cp95	Initial (beats/min)	66.9	65.8	63.2	65.0	64.7
	% change of HR	9†	7.6	4.7	3.1	0.0
Intubation						
sBP at Cp50	Initial (mmHg)	92.3	92.8	95.5	90.6	88.7
	% change of sBP	24.5†	19.5†	15.0†	12.0	7.2
sBP at Cp95	Initial (mmHg)	70.3	79.6	86.4	78.0	74.8
	% change of sBP	28.7†	20.2†	11.9†	7.8	2.0
HR at Cp50	Initial (beats/min)	83.7	70.3	64.9	62.1	60.9
	% change of HR	20.3†	8.5†	7.7	4.8	3.3
HR at Cp95	Initial (beats/min)	65.2	60.4	60.8	61.4	56.5
	% change of HR	19.9†	13.2†	4.8	3.3	1.8
Skin incision						
sBP at Cp50	Initial (mmHg)	101.3	102.7	104.8	99.6	106.3
	% change of sBP	18.6†	11.7†	9.7†	5.3	1.0
sBP at Cp95	Initial (mmHg)	86.1	90.0	92.0	91.7	96.8
	% change of sBP	21.2†	14.5†	7.4†	4.6	0.6
HR at Cp50	Initial (beats/min)	76.2	70.1	67.4	66.1	71.0
	% change of HR	14.4†	4.0	3.8	2.7	0.5
HR at Cp95	Initial (beats/min)	66.2	64.8	61.3	61.6	65.7
	% change of HR	10.6†	7.7†	5.4	3.2	−0.2

*The patients who required atropine or ephedrine because of bradycardia or hypotension were excluded.

†$P < 0.05$, significant difference from tetanus.

of allowing only one measurement per patient and of possibly not being representative of all noxious stimuli encountered in surgical operations. Skin incision is nearly impossible to standardize because the response depends entirely on the size and place of the incision.[20] Determination of whether a reaction is positive may be subjective because not all reactions may be classified into "gross purposeful movement" as established in the original MAC concept.[23] Our study also demonstrates that skin incision is clearly not the most intense stimulus.

Determining MAC_{EI} (end-tidal concentration of a gas needed by 50% of the population to prevent all movement during and immediately after endotracheal intubation) is of clinical value because there are a number of surgical situations that demand a level of anesthesia that not only allows adequate conditions for laryngoscopy but also prevents subsequent coughing or "bucking." Mechanical stimulation of lower tracheal or carinal reflexes caused by the endotracheal tube or by the sudden, irritative flow of dry gases to these areas probably produces such events. The present study showed that

Table 4. Results of Multiple Regression Used to Evaluate the Influence of Fentanyl Concentration, Propofol Concentration, and the Response to the Various Stimulation on the Degree of the Absolute Rise of Systolic Blood Pressure (mmHg) and Heart Rate (beats/min)

Effect to Be Tested by Multiple Regression	Correlation Coefficient†	
	Increase of Blood Pressure	Increase of Heart Rate
Tetanus (n = 421)		
Fentanyl concentration (ng/ml)	0.15	0.14
Propofol concentration (μg/ml)	0.11	0.09
Response (positive = 1, negative = 0)	0.12	0.1
Laryngoscopy (n = 320)		
Fentanyl concentration (ng/ml)	0.29	0.2
Propofol concentration (μg/ml)	0.11	0.09
Response (positive = 1, negative = 0)	0.17	0.14
Intubation (n = 299)		
Fentanyl concentration (ng/ml)	0.57	0.34
Propofol concentration (μg/ml)	0.19	0.12
Response (positive = 1, negative = 0)	0.23	0.19
Skin incision (n = 114)		
Fentanyl concentration (ng/ml)	0.45	0.3
Propofol concentration (μg/ml)	0.13	0.08
Response (positive = 1, negative = 0)	0.21	0.12

*The patients who required atropine or ephedrine because of bradycardia or hypotension were excluded.

†Blood pressure and heart rate increase at Cp50 of each stimulation (see also table 3 and figs. 6A, 6B, 6C, and 6D).

laryngoscopy followed by intubation was the strongest stimulus, confirming the results of previous studies.[20,24,25] The $Cp_{50intubation}$-to-$Cp_{50skin\ incision}$ ratio was between 1.7 and 1.9 either in propofol alone or in propofol with fentanyl, which was higher than 1.51 in isoflurane[20] and lower than 2.17 in alfentanil with 66% nitrous oxide.[24]

Each stimulation has to be performed in the nonparalyzed patient if motor response is to be evaluated. Stimuli of laryngoscopy and intubation may be difficult to use in the nonparalyzed patient because they may provoke laryngospasm.[20] The technique of inducing general anesthesia solely with an inhalation agent is frequently used in pediatric patients.[26] With sufficient anesthetic depth, tracheal intubation may also be accomplished in adults. In the absence of a neuromuscular blocking drug, certain other anesthetic drugs are known to obtund the laryngeal reflex.[27-29] Propofol has been shown to be a more effective tracheal relaxant *in vitro* than ketamine.[30] Visualization of the vocal cords with standard laryngoscopy is often possible without a muscle relaxant after propofol. We frequently observed widely abducted immobile vocal cords during laryngoscopy, and our patients had no episodes of laryngospasm that needed to be treated with other drugs in this study.

The systolic blood pressure response to stimulation was influenced most by the fentanyl concentration (table 4). The attenuation of systolic blood pressure and heart rate increase by propofol was made obvious in a dose-dependent fashion after each of stimulation when propofol was simultaneously used with fentanyl (Table 2). Although this tendency was uniform, it did not reach high correlation coefficient in this study (table 4). When propofol was used alone, blood pressure and heart rate after stimulation may increase considerably even at propofol concentrations greater than those needed to obtund motor reaction as shown in Group 1 (figs. 4A-D). In patients who suffer, for example, from coronary heart disease, such hemodynamic responses may be dangerous. The clinical implication of this finding is that propofol should be better to use with fentanyl rather than used as a sole agent; 6.4 μg/ml of propofol, corresponding to the dose producing loss of verbal command in 95% of subjects with 2.6 ng/ml of fentanyl, may induce a lower degree of hypertension after intubation relative to that induced at 7.8 μg/ml of propofol, corresponding to the dose producing loss of verbal command in 95% of subjects without fentanyl (table 2 and fig. 4C). The two concentrations of propofol with and without fentanyl induced the same degree of hypotension before intubation. The lack of motor response is not an accurate predictor of the ability of an agent to depress hemodynamic reaction.

In summary, we defined the propofol concentration required to abolish somatic and hemodynamic responses to verbal command, tetanic stimulation, laryngoscopy, intubation, and skin incision. Tracheal intubation was the strongest stimulus. The $Cp_{50intubation}$-to-$Cp_{50skin\ incision}$ ratios were between 1.7 and 1.9 either in group given propofol alone or in the group given propofol with fentanyl. Hemodynamic reaction showed a large interindividual variability. The systolic blood pressure response was influenced most by the fentanyl concentration in each of noxious stimuli. Propofol used as a sole agent depresses prestimulation blood pressure, but the blood pressure response *per se* to stimulation was virtually concentration-independent. Propofol with fentanyl was able to suppress motor and hemodynamic

reactions to various noxious stimuli, although correlation between somatic response and hemodynamic response to noxious stimuli was poor.

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