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Hemodynamic Response to Induction and Intubation

Propofol/Fentanyl Interaction

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Background: **When given as an intravenous bolus for induction of anesthesia, propofol can decrease postintubation hypertension but can also create moderate to severe postinduction, preintubation hypotension. The addition of fentanyl usually decreases the postintubation hypertension but can increase the propofol-induced preintubation hypotension. The goal of the study was to determine the relation between propofol and fentanyl doses and the hemodynamic changes postinduction, preintubation and postintubation.**

Methods: **Twelve groups of 10 patients, ASA physical status 1 or 2, first received fentanyl 0, 2, or 4 $\mu g \cdot kg^{-1}$ and then 5 min later received propofol 2.0, 2.5, 3.0, or 3.5 $mg \cdot kg^{-1}$ as an intravenous bolus for induction of anesthesia. Arterial blood pressure was continuously monitored. The trachea was intubated 4 min after propofol administration.**

Results: **The mean decrease in systolic blood pressure after propofol was 28 mmHg when no fentanyl was given, 53 mmHg after 2 $\mu g \cdot kg^{-1}$ of fentanyl ($P < 0.05$ *vs.* no fentanyl), and 50 mmHg after 4 $\mu g \cdot kg^{-1}$ ($P < 0.05$ *vs.* no fentanyl; no statistically significant difference 4 *vs.* 2 $\mu g \cdot kg^{-1}$). There was no statistically significant difference in hemodynamic response to intubation relative to propofol dose. Hemodynamic response to intubation was decreased by the administration of fentanyl; the mean increase of systolic blood pressure after intubation was 65 mmHg from preintubation value without fentanyl, 50 mmHg after 2 $\mu g \cdot kg^{-1}$, and 37 mmHg after 4 $\mu g \cdot kg^{-1}$ ($P < 0.05$ for 2 and 4 $\mu g \cdot kg^{-1}$ *vs.* no fentanyl and for 4 *vs.* 2 $\mu g \cdot kg^{-1}$). Hemodynamic changes postintubation were not statistically different with increasing doses of propofol.**

Conclusions: **Hemodynamic changes after induction with propofol or propofol/fentanyl, pre- or postintubation, are not modified when the propofol dose is increased from 2 to 3.5 $mg \cdot kg^{-1}$. Maximal hypotension preintubation occurs with a fentanyl dose of 2 $\mu g \cdot kg^{-1}$, whereas the magnitude of postintubation hypertension is significantly decreased with an increase in the fentanyl dose to 4 $\mu g \cdot kg^{-1}$. (Key words: Anesthetics, intravenous: propofol, fentanyl; Hemodynamics: response to intubation; Interactions: drug.)**

PROPOFOL is commonly used for the induction of anesthesia. The recommended intravenous bolus induction dose is 2.5 $mg \cdot kg^{-1}$, corresponding to the dose producing loss of consciousness in 95% of subjects.[1,2] This dose may induce, before intubation, a greater degree of hypotension relative to other hypnotic agents.[3] This dose does not suppress the hypertensive response to intubation.[4,5] Decreasing the rate of propofol administration can minimize both the hemodynamic changes before intubation and the total propofol dose required to achieve loss of consciousness.[6] The influence of different propofol doses on the hemodynamic response to intubation has not been systematically studied.

The addition of fentanyl for induction is used to provide analgesia during surgical procedures[7] and to decrease the hypertensive response to intubation.[8–10] When given with propofol, fentanyl can increase the preintubation hypotension.[3,5] The influence of propofol and fentanyl dose on the amplitude of the pre- and postintubation hemodynamic changes has not been described.

The goals of this study were as follows:

- to estimate how changing the propofol dose from 2.0 to 3.5 $mg \cdot kg^{-1}$ modifies the hemodynamic response to the stimulation of intubation

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- to estimate how the addition of fentanyl 2 or 4 $\mu g \cdot kg^{-1}$ modifies the hemodynamic response to the stimulation of intubation
- to measure the consequences of these propofol and fentanyl dose changes on preintubation hypotension
- to describe the interaction of propofol and fentanyl dose on these hemodynamic responses postinduction, preintubation, and postintubation.

Materials and Methods

Patients undergoing elective oncologic surgery, ASA physical status 1 or 2, aged 18–65 yr, were studied. The patients were excluded if they were receiving cardiovascular medication or had received any recent chemotherapy. They were excluded if one or more of the following disease states were present: hypertension, cardiac, coronary, respiratory, renal or cerebral disease, intestinal obstruction, cachexia or dehydration. They were also excluded if Allen's test was abnormal, or if intubation was expected to be difficult. The study was approved by the hospital ethics committee. On the day before surgery, all patients gave informed, written consent and were randomly allocated to 1 of 12 groups (table 1) according to the propofol dose (2.0, 2.5, 3.0 or 3.5 $mg \cdot kg^{-1}$) and fentanyl dose (0, 2 or 4 $\mu g \cdot kg^{-1}$). Randomization was stratified to obtain a sex ratio of 2:1 for women to men, reflecting the gender makeup of our surgical patient population.

All patients were nonpremedicated on the day of surgery. In the operating room, an arm vein and radial artery were cannulated under local anesthesia (Terumo Surflo catheter 18G and 20G). Arterial blood pressure was monitored *via* a quartz transducer (Hewlett-Packard 1290A0PTOO6, Boeblingen, West Germany) connected to the monitor (Hewlett-Packard 78342A). Monitoring by electrocardiography and pulse oximetry also was established. All patients received a fluid load of Ringer's lactate 5 $ml \cdot kg^{-1}$ over a 15-min period.

The patients were then given fentanyl or a placebo by 2 ml of normal saline as an intravenous bolus. Five minutes later, propofol was administered manually at a rate of 5 $mg \cdot s^{-1}$, and vecuronium 0.1 $mg \cdot kg^{-1}$ was given as a rapid intravenous bolus (15 s) to facilitate intubation. The patients' lungs were manually ventilated for 4 min with 100% oxygen before orotracheal intubation was performed. The patients' lungs were then mechanically ventilated with a tidal volume of 8 $ml.kg^{-1}$, a respiratory rate of $12.min^{-1}$, and 100% oxygen for 3 min before any additional anesthetic was given. Both the patient and the resident who performed intubation were blind to the doses of drugs administered.

Table 1. Patient Demographics

Fentanyl Dose (μg/kg)	Propofol Dose (mg/kg)	Sex Ratio (F/M)	Age (yr)	Weight (kg)
0	2	7/3	44 ± 9 (32–56)	65 ± 13 (52–90)
0	2.5	6/4	41 ± 10 (22–55)	71 ± 14 (49–95)
0	3	6/4	46 ± 11 (23–62)	64 ± 9 (52–80)
0	3.5	7/3	40 ± 11 (22–59)	66 ± 16 (48–94)
2	2	7/3	50 ± 10 (33–65)	62 ± 14 (45–88)
2	2.5	7/3	44 ± 13 (21–64)	68 ± 14 (48–95)
2	3	6/4	48 ± 13 (27–65)	65 ± 13 (47–95)
2	3.5	7/3	43 ± 14 (29–63)	60 ± 12 (40–76)
4	2	7/3	46 ± 9 (31–62)	59 ± 9 (45–80)
4	2.5	7/3	50 ± 8 (37–61)	62 ± 6 (54–75)
4	3	6/4	46 ± 11 (21–60)	66 ± 14 (47–98)
4	3.5	7/3	44 ± 10 (22–56)	62 ± 13 (40–85)

Values are mean ± SD (range); n = 10 patients/group.

Data Recording

Heart rate, systolic and diastolic blood pressure were continuously recorded on an analogue recorder (Gould ES1000, Ballainvilliers, France). Numeric values were averaged over a 10-s period to minimize the influence of respiratory variations.

The hemodynamic response to the induction of anesthesia, before intubation was defined for each patient as follows: preintubation value (4 min after the end of propofol, just before laryngoscopy for intubation) minus preinduction value (5 min after fentanyl, just before the beginning of propofol). The hemodynamic response to intubation was defined as follows: postintubation value (1 min after the beginning of laryngoscopy) minus preintubation value previously defined. Fentanyl or propofol plasma concentrations were not measured. Instead, we calculated for each patient the predicted fentanyl and propofol concentrations, in both plasma and biophase (*i.e.*, effect site),

every minute during the study time using literature pharmacokinetic data.[11]

Statistical Analysis

All results are expressed as mean ± standard deviation. In each group (corresponding to one propofol dose and one fentanyl dose), we studied time variations of systolic blood pressure, diastolic blood pressure and heart rate by analysis of variance (ANOVA) for paired values. When ANOVA was significant, we compared all times to baseline and postintubation to preintubation values by both Ryan-Eynot-Gabriel-Welsch multiple F test, and Bonferroni *t* tests.[12] When a discrepancy was found between the signification level, the worst (highest) signification level was reported in the result. The influence of fentanyl and propofol doses on the hemodynamic responses to induction and intubation previously defined was studied by two-factor ANOVA followed by multiple regression with type III adjustment (each drug adjusted to the dose of the other).[12] The interaction between fentanyl and propofol was estimated by the product of fentanyl dose by propofol dose. Only linear models were studied, as follows:

$$\text{Response} = a + bF_{dose} + cP_{dose} + dF_{dose} \times P_{dose}$$

where F_{dose} = the fentanyl dose in micrograms per kilogram and P_{dose} = the propofol dose in milligrams per kilogram. $P < 0.05$ was considered to represent a statistically significant difference. Confidence intervals (CI) for a, b, c, and d parameters were estimated with a 95% confidence level. Statistical analysis was performed using SAS 6.06 program (VAX-VMS).

Results

During a 12-month period, 120 patients were studied, 10 patients in each group. Seven additional patients were excluded: 5 of them before induction because of failure to insert the arterial catheter and 2 during induction of anesthesia: 1 because of profound bradycardia (heart rate 35 beats/min) after fentanyl 2 $\mu g \cdot kg^{-1}$ and propofol 3 $mg \cdot kg^{-1}$, which required atropine; and 1 because of severe hypotension (systolic blood pressure < 50 mmHg) after fentanyl 4 $\mu g \cdot kg^{-1}$ and propofol 2.5 $mg \cdot kg^{-1}$, which required ephedrine. The latter 2 patients were excluded from the analysis because we considered that the cardiovascular medication they received modified the hemodynamic response we evaluated in this study. No significant difference was found among the groups concerning age, sex ratio, weight (table 1), or blood pressure and heart rate baseline values (tables 2 and 3).

Hemodynamic Effect of Fentanyl: Preinduction

During the 5-min period preceding propofol administration, no significant changes occurred in systolic blood pressure, diastolic blood pressure or heart rate for fentanyl doses of 0, 2 or 4 $\mu g \cdot kg^{-1}$ (figs. 1 and 2 and tables 2 and 3).

Hemodynamic Effect of Propofol: Postinduction, Preintubation

Time Effect. When propofol was given without fentanyl (fig. 1A), systolic blood pressure decreased significantly in only two groups (propofol 3.0 and 3.5 $mg \cdot kg^{-1}$). The decrease in diastolic blood pressure was not significant. When given with fentanyl, irrespective of the propofol dose, an early decrease in systolic and diastolic blood pressure occurred (figs. 1B and 1C). Systolic and diastolic blood pressure became significantly lower than baseline values from the end of administration in two groups (fentanyl 4 $\mu g \cdot kg^{-1}$, propofol 2.5 or 3.5 $mg \cdot kg^{-1}$) and 1 min later in the six other groups. After this decrease, blood pressure remained stable until the time of intubation (fig. 1 and table 2). Heart rate increased temporarily, but nonsignificantly, during propofol injection (fig. 2), probably

Table 2. Systolic Blood Pressure (mmHg) *Versus* Clinical Events

Fentanyl Dose (μg/kg)/ Propofol Dose (mg/kg)	Baseline	After Fentanyl, before Propofol	After Propofol, before Intubation	After Intubation
0/2*	126 ± 12	126 ± 14	110 ± 19	186 ± 23†‡
0/2.5*	132 ± 15	131 ± 14	114 ± 18	170 ± 26†‡
0/3*	144 ± 11	142 ± 10	114 ± 9†	192 ± 31†‡
0/3.5*	140 ± 14	140 ± 13	113 ± 12†	164 ± 19†‡
2/2*	147 ± 14	146 ± 22	87 ± 11†	131 ± 32‡
2/2.5*	148 ± 16	141 ± 13	87 ± 11†	153 ± 25‡
2/3*	137 ± 14	132 ± 15	77 ± 12†	117 ± 29‡
2/3.5*	141 ± 20	136 ± 18	91 ± 22†	141 ± 40‡
4/2*	138 ± 18	134 ± 13	89 ± 14†	127 ± 19‡
4/2.5*	147 ± 27	137 ± 31	81 ± 8†	106 ± 16†‡
4/3*	148 ± 25	142 ± 28	90 ± 22†	136 ± 42‡
4/3.5*	138 ± 15	136 ± 16	88 ± 10†	124 ± 20‡

Values are mean ± SD.

* $P < 0.001$ by ANOVA.

† $P < 0.05$ *versus* the baseline value in the same group.

‡ $P < 0.05$ *versus* the preintubation value.

Table 3. Heart Rate (beats/min) *Versus* Clinical Events

Fentanyl Dose (μg/kg)/ Propofol Dose (mg/kg)	Baseline	After Fentanyl, before Propofol	After Propofol, before Intubation	After Intubation
0/2*	86 ± 17	82 ± 17	76 ± 16	99 ± 15‡
0/2.5*	83 ± 12	81 ± 14	80 ± 12	99 ± 10‡
0/3†	82 ± 14	79 ± 17	82 ± 12	96 ± 17
0/3.5	88 ± 19	86 ± 20	84 ± 16	96 ± 13
2/2†	84 ± 12	78 ± 11	66 ± 11	74 ± 15
2/2.5	84 ± 18	80 ± 22	68 ± 15	82 ± 17
2/3	85 ± 20	81 ± 18	70 ± 12	81 ± 11
2/3.5	90 ± 24	86 ± 21	76 ± 14	91 ± 20
4/2	78 ± 14	69 ± 8	67 ± 6	73 ± 8
4/2.5	79 ± 13	72 ± 12	66 ± 12	70 ± 11
4/3†	79 ± 9	74 ± 15	65 ± 8	84 ± 25
4/3.5	75 ± 18	68 ± 13	63 ± 9	73 ± 15

Values are mean ± SD.

* $P < 0.01$ by ANOVA.

† $P < 0.05$ by ANOVA.

‡ $P < 0.05$ *versus* the preintubation value.

as a result of the pain on injection that several patients experienced. Heart rate remained stable until intubation (fig. 2 and table 3).

Dose Effect: Interaction of Fentanyl and Propofol. For a given dose of fentanyl, the propofol-induced decrease in systolic and diastolic blood pressure was not related to the dose of propofol (figs. 1 and 3). For a given dose of propofol, the administration of fentanyl resulted in a significant decrease in systolic blood pressure. However, there was no difference between the 2 and 4 $\mu g \cdot kg^{-1}$ doses of fentanyl. No interaction of fentanyl and propofol dose was statistically detected. The fentanyl-induced decrease in systolic blood pressure was not linearly related to the fentanyl dose (fig. 3). There was no statistically significant effect of fentanyl or propofol dose on heart rate changes after induction.

Hemodynamic Response to Intubation Stimulus

Time Effect. Intubation was associated with a significant increase in systolic and diastolic blood pressure in all groups (fig. 1). Systolic and diastolic blood pressure exceeded preinduction values only in the four groups that did not receive fentanyl and remained significantly lower than the baseline values in one group (fentanyl 4 $\mu g \cdot kg^{-1}$, propofol 2.5 $mg \cdot kg^{-1}$). Systolic and diastolic blood pressure postintubation were not significantly different from the baseline values in the seven other groups (table 2). Heart rate increased significantly only in two of four groups not receiving fentanyl (propofol 2 or 2.5 $mg \cdot kg^{-1}$, fig. 2A). Heart rate, postintubation, did not exceed baseline value in any group (table 3).

Dose Effect: Interaction of Fentanyl and Propofol. No significant influence of propofol dose was observed on the hemodynamic response to intubation: increasing the propofol dose from 2 to 3.5 $mg \cdot kg^{-1}$ did not prevent or modify the degree of the hypertensive response to intubation. There was a dose-dependent effect of fentanyl on decreasing the hemodynamic response to intubation (fig. 4). The interaction of fentanyl and propofol on systolic blood pressure changes

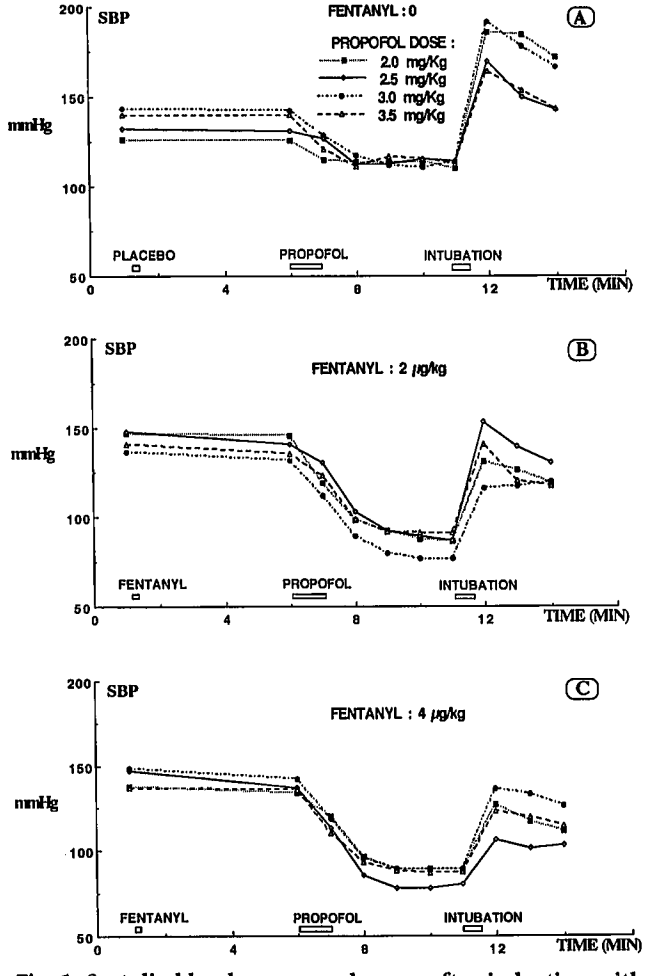

Fig. 1. Systolic blood pressure changes after induction with propofol plus placebo (*A*) or 2 $\mu g \cdot kg^{-1}$ fentanyl (*B*) or 4 $\mu g \cdot kg^{-1}$ fentanyl (*C*) and intubation. Data are means; n = 10 patients per data point. See table 2 for standard deviations.

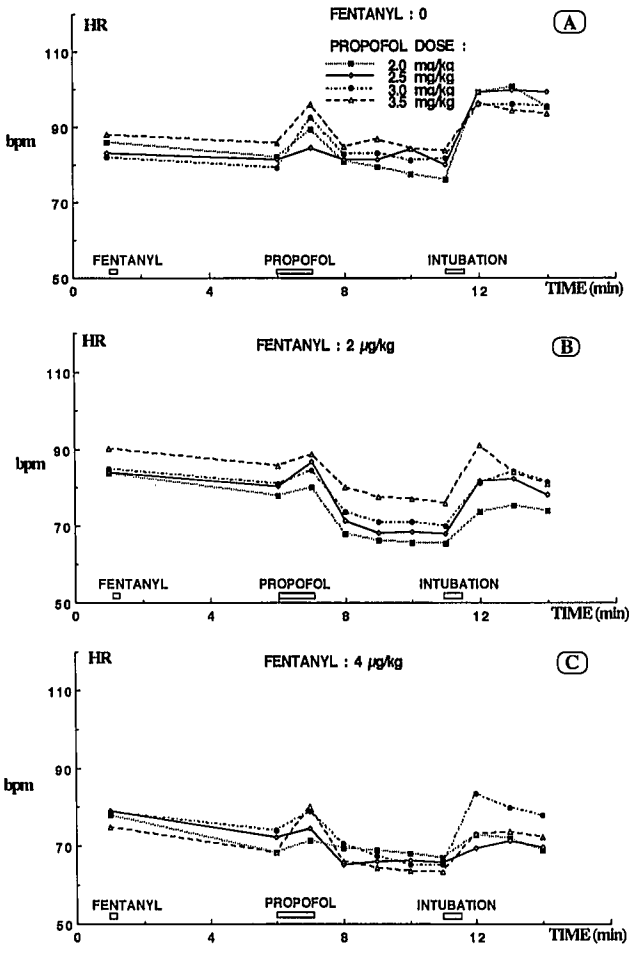

Fig. 2. Changes in heart rate after induction with propofol plus placebo (*A*) or 2 $\mu g \cdot kg^{-1}$ fentanyl (*B*) or 4 $\mu g \cdot kg^{-1}$ fentanyl (*C*) and intubation. Data are means; n = 10 patients per data point. See table 3 for standard deviations.

was statistically significant by ANOVA. However, after multiple regression, this interaction could not be characterized with a linear model regression as described in the methods.

Fentanyl had a dose-dependent effect on the heart rate response to intubation (fig. 4), and a statistically significant interaction was found by ANOVA. After multiple regression, this dose–effect relation could be described by the following linear model:

Heart rate response to intubation (beats per minute)

$$= 32 - 10.6F_{dose} - 5.7P_{dose} + 3.1F_{dose} \times P_{dose}$$

The CIs for the four parameters of this model were as follows: for a = 32, CI = 14.9, 50.5; for b = −10.6, CI = −17.5, −3.7; for c = −5.7, CI = −12, 0.6; for d = 3.1, CI = 0.7, 5.6.

Predicted Plasma and Biophase Concentrations

Figure 5 displays the predicted plasma and biophase concentrations of fentanyl and propofol for the different drug doses given in the protocol. The 5-min period before induction was adequate to reach a phase of slow decrease for both plasma and biophase fentanyl concentrations (fig. 5A). After induction with propofol and before intubation, maximal predicted propofol biophase concentrations were also achieved within 2.3 min in all groups (fig. 5B). This delay was similar to the time required to achieve the maximal blood pres-

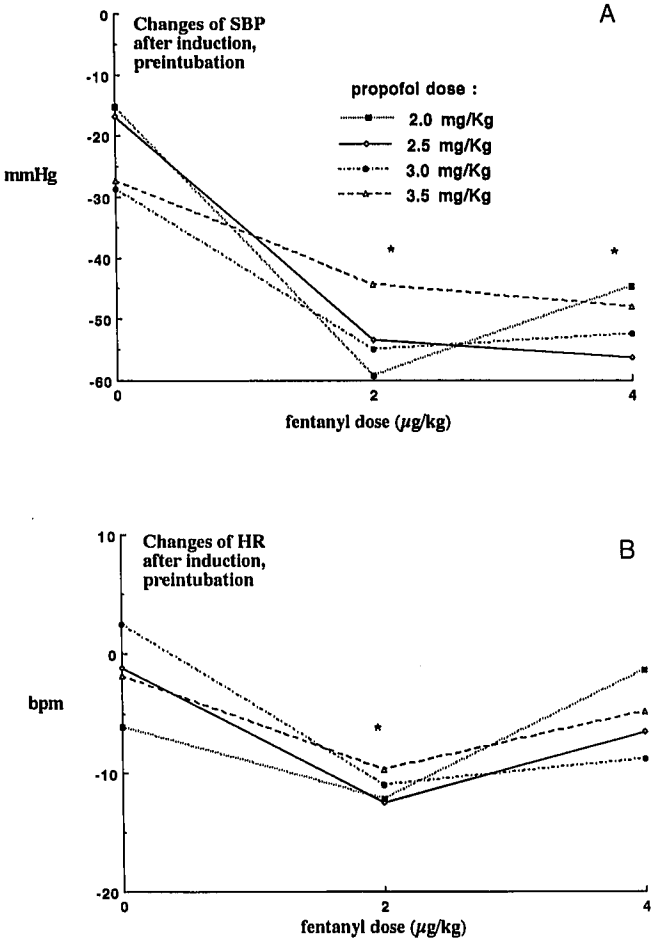

Fig. 3. Changes in systolic blood pressure (SBP, *A*) and heart rate (HR, *B*) after induction, before intubation, relative to fentanyl and propofol doses. Data are means; n = 10 patients per data point. *Fentanyl dose of 0 *versus* 2 or 4 $\mu g \cdot kg^{-1}$, $P < 0.05$.

sure changes (fig. 1). However, both plasma and biophase propofol concentrations then decreased from that time to intubation whereas blood pressure remained stable. At the beginning of the laryngoscopy before intubation, predicted fentanyl biophase concentrations ranged from 2.0 to 4.0 ng · ml^{-1} in the 2- and 4-μg · kg^{-1} doses, whereas predicted fentanyl plasma concentrations were 1.2 and 2.4 ng · ml^{-1} respectively. Also at the time of intubation, predicted propofol biophase concentrations were 2.8, 3.6, 4.2 and 4.6 μg.ml^{-1} for the 2.0, 2.5, 3.0, and 3.5 mg · kg^{-1} doses, with predicted propofol plasma concentrations of 1.0, 1.2, 1.4, and 1.6 μg · ml^{-1}.

Discussion

The goal of this study was to examine the interaction of fentanyl and propofol, when given at doses clinically useful in anesthetic practice, on hemodynamic changes after induction of anesthesia before and after the noxious stimulation of laryngoscopy and intubation. To characterize the relative influence of propofol and fentanyl, specific study-design methods were necessary.

Fentanyl was administered before propofol to quantitate separately its hemodynamic effects. Propofol was given only when the maximal effect of fentanyl was assumed to be achieved, and intubation was performed after the maximal expected effect of propofol had been achieved.

We used a computer simulation of the biophase drug concentration to define the time of the maximal expected effect. After intravenous bolus doses, there is a lag between changes in the plasma concentration and the corresponding changes in the central nervous system (CNS) effect because of the blood–CNS equilibration time. The maximal pharmacodynamic effect is achieved after the peak plasma concentration.[13] Thus, for both fentanyl and propofol, the predicted plasma concentration may not be closely correlated to the drug effect. The biophase (or effect-site) concentration is calculated by a mathematical fitting from the plasma concentration *versus* effect curve and the relation between the plasma and the biophase concentrations is characterized by a time constant (ke0).[14] The biophase concentration reflects the steady-state plasma concentration that would induce the same degree of drug effect. It is designed to be closely correlated to this effect.

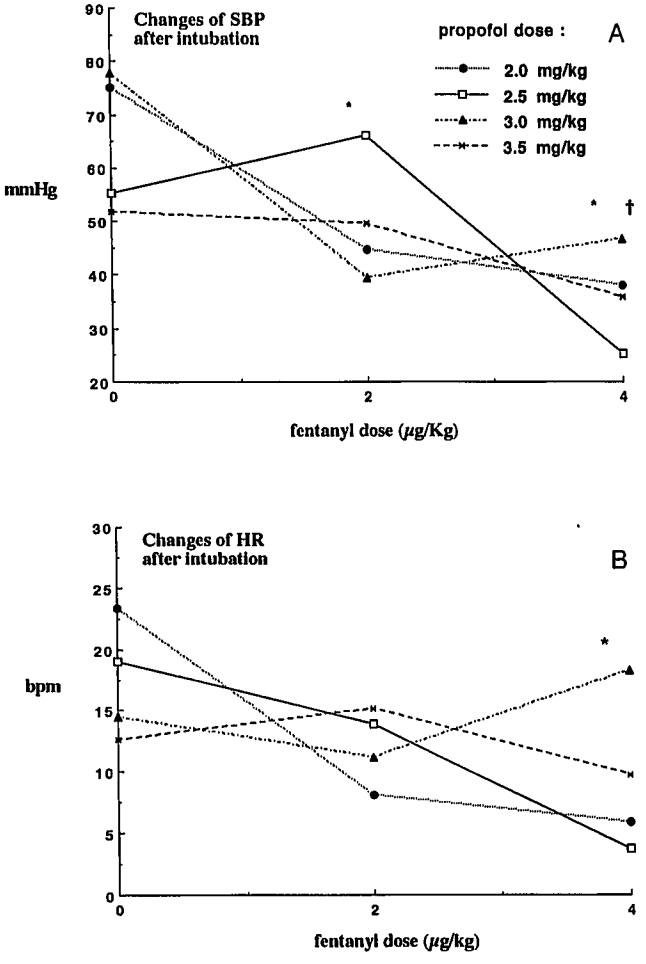

Fig. 4. Changes in systolic blood pressure (SBP, *A*) and heart rate (HR, *B*) after intubation, relative to propofol and fentanyl doses. Data are means; n = 10 patients per data point. *Fentanyl dose of 0 *versus* 2 or 4 μg · kg^{-1}, $P < 0.05$. †Fentanyl dose of 2 *versus* 4 μg · kg^{-1}, $P < 0.05$.

We used CNS as the biophase to predict biophase concentrations because the CNS ke0 was the only one published for both drugs with similar methodology when we started the study. Also, we assumed that the hemodynamic response to noxious stimuli may be related to the CNS effect of the drugs. The ke0, determined for CNS by electroencephalography, was 2.9 min for propofol,[15] whereas that for fentanyl was 6.4 min.[16] Recently, Dyck and colleagues‖ in our laboratory determined the ke0 for hemodynamic effects of propofol, without any noxious stimulation, to be 5.9 min. As the time to achieve maximal effect depends on both the ke0 and the distribution pharmacokinetic parameters,[13] the choice of the hemodynamic ke0 for propofol, with

‖ Dyck JB: Personal communication.

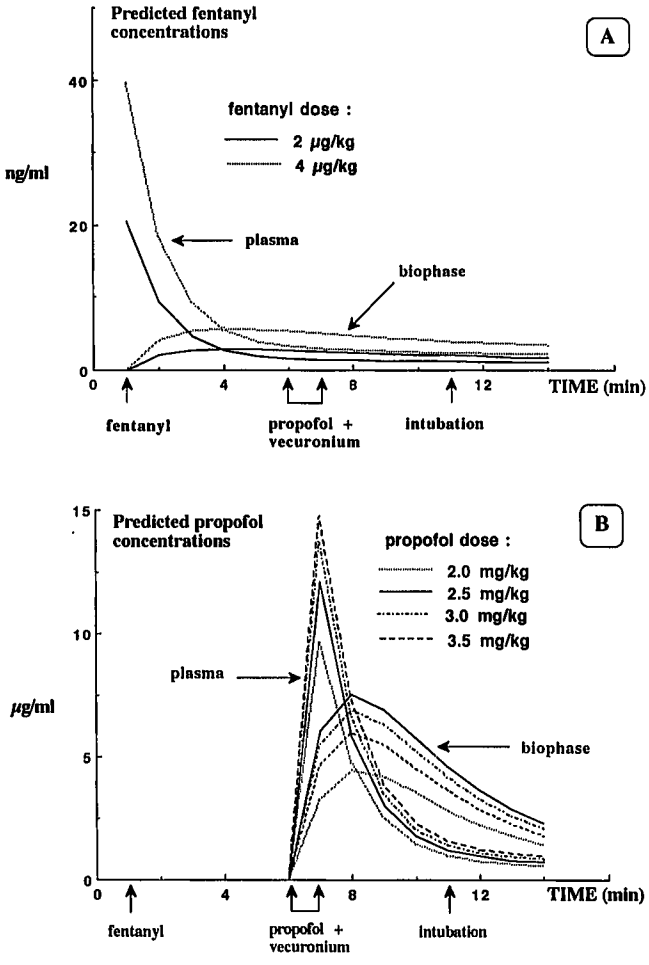

Fig. 5. Predicted fentanyl (*A*) and propofol (*B*) concentrations in plasma and biophase. Simulated values for each patient according to previously published pharmacokinetic parameters. Data are means; n = 40 patients per fentanyl dose and n = 30 patients per propofol dose.

the same pharmacokinetic parameters would have increased the time to achieve the expected maximal effect by only 35 s (2.8 *vs.* 2.3 min). The 5-min delay between fentanyl and subsequent propofol administration was sufficient to achieve a plateau of the predicted fentanyl biophase concentration. This should have resulted in a constant fentanyl drug effect during the subsequent induction. The peak of the predicted propofol biophase concentration occurred at 2.3 min after propofol administration. We performed intubation 4 min after propofol administration to achieve the same maximal muscle relaxation in all patients. During this time, there was minimal decline of the propofol biophase concentration.

Hemodynamic Effect of Fentanyl: Preinduction

Fentanyl given before propofol had no detectable hemodynamic effects. This result is not surprising; previous studies in which larger doses (50–100 $\mu g \cdot kg^{-1}$) were given did not reveal significant changes in blood pressure.[17,18] Bradycardia has been described in dogs,[19] also after high doses (20–100 $\mu g \cdot kg^{-1}$), but that finding was not constant in human studies.[17,18] One patient, however, was excluded from our study because of profound bradycardia.

Hemodynamic Effect of Propofol and Fentanyl: Postinduction, Preintubation

Time Effect. A decrease in blood pressure after propofol administration has been seen in other studies.[4] The continuous recording of arterial blood pressure allowed excellent resolution of this hemodynamic depression in our study. Had blood pressure been measured with a noninvasive intermittent method, it would not have been possible to resolve the hemodynamic depression seen in this study to the same degree.

Dose Effect. After administration of propofol doses identical or higher than the initially suggested dose effective in 95% of subjects for induction of anesthesia,[1,2] we observed the same hemodynamic response irrespective of the administered dose. This suggests that at a propofol dose of 2 $mg \cdot kg^{-1}$, the maximal hypotensive hemodynamic effect was achieved.

Without opioids, only a few studies have compared the hemodynamic changes after variable doses of propofol before stimulation. Mulier *et al.*[20] compared 1.5 and 2.5 $mg \cdot kg^{-1}$ given as a bolus and found the systolic blood pressure decrease to be 19% *versus* 27%. Van Hemelrijck *et al.*[21] observed dose-dependent hemodynamic effects with 3 *versus* 6 *versus* 12 $mg \cdot kg^{-1} \cdot h^{-1}$ on baboons. Blake *et al.*[22] compared 12 *versus* 24 *versus* 36 $mg \cdot kg^{-1} \cdot h^{-1}$ on rabbits and did not find any difference relative to the propofol infusion rate; this again suggests that a maximal effect can be achieved from the infusion rate of 12 $mg \cdot kg^{-1} \cdot h^{-1}$.

With fentanyl (0.75 $\mu g \cdot kg^{-1}$), Peacock *et al.*[6,23] compared 3 infusions rates of propofol, given to the end point of loss of consciousness. They demonstrated that slowing the infusion rate of propofol to 300 *versus* 600 or 1,200 $ml \cdot h^{-1}$ decreased the hemodynamic response to induction for the lower dose, without statistically significant difference between the two higher doses: the decrease in systolic blood pressure was 19% *versus* 25% or 27%. Thus, without or with opioid, the hemodynamic effect of propofol before stimulation ap-

pears to be nonlinear with the propofol dose. Our results suggest that this maximal hemodynamic effect can be achieved from a propofol bolus dose of 2 $mg \cdot kg^{-1}$.

However, the maximal blood pressure decrease from propofol was only achieved when fentanyl was added. This supports previous studies about the role of opioids, and especially fentanyl, on increasing blood pressure changes after propofol. Comparisons of induction by propofol without and with fentanyl observed a greater degree of hypotension with fentanyl[3,5]; Fentanyl added 15 min after propofol increased the mean blood pressure decrease from 15% to 47%.[24] All protocols where blood pressure did not change significantly did not administer any opioid for premedication or induction.[22,25] Conversely, all of the protocols providing a systolic blood pressure decrease of 30% or more did have an opioid present for premedication[26,27] or for anesthesia.[5,24,28]

Whereas the influence of fentanyl to potentiate propofol hemodynamic depression has been described, the influence of the fentanyl dose has not been studied. The lack of difference in the hemodynamic response between 2 and 4 $\mu g \cdot kg^{-1}$ fentanyl suggests that there may be a maximal effect of fentanyl in decreasing blood pressure with propofol. With the protocol of administration described in our methods, this maximal effect can be achieved with a dose lower than 2 $\mu g \cdot kg^{-1}$. The amplitude of the blood pressure changes, similar to the maximal changes previously described, supports this assumption.[4] We also observed an interaction between fentanyl and propofol: the hemodynamic effect was relative to the presence of fentanyl but appeared only after propofol administration. This interaction was not dependent on the dose, by ANOVA statistical analysis. The mechanism of the blood pressure decrease after propofol or propofol/fentanyl is still debated.# Decrease in both systemic vascular resistances[5,29-31] and cardiac output[5,24,32,33] and impairment of baroreflexes[22,34] have been described.

Hemodynamic Response to Intubation

In all groups, whatever the fentanyl and propofol doses, blood pressure increased after intubation. We demonstrated that increasing propofol dose from 2 to 3.5 $mg \cdot kg^{-1}$ did not modify this hemodynamic response. This is consistent with a previous study by Coates *et al.*[26] who compared response to intubation after two protocols of infusion (propofol 2 $mg \cdot kg^{-1}$ bolus followed by an infusion of either 54 or 108 $\mu g \cdot kg^{-1} \cdot min^{-1}$). They observed the same hemodynamic response to intubation for the two rates, similar to our observation of the same hemodynamic response for our four intravenous bolus doses. Conversely, autonomic response to surgical stimulation (defined as blood pressure or heart rate change, lacrimation or diaphoresis) could be suppressed by an infusion of propofol providing mean blood propofol concentrations of 2.97 $\mu g \cdot ml^{-1}$ for minor surgery, and 4.05 $\mu g \cdot ml^{-1}$ (associated with meperidine intravenous bolus), for major surgery.[35] These concentrations are similar to the predicted biophase concentrations for the doses used in our study. This suggests that the depth of anesthesia provided by propofol is not the main factor of the hemodynamic response to intubation. The level of analgesia provided by opioids appears to be a major factor that requires more quantitation.

The effect of fentanyl on preventing hemodynamic response to intubation has already extensively been described. Large doses of fentanyl used alone (50–100 $\mu g \cdot kg^{-1}$) suppressed the hemodynamic response to orotracheal intubation.[17,36] When associated with thiopental, a fentanyl dose of 5 $\mu g \cdot kg^{-1}$ decreased the blood pressure response to intubation,[8] and a dose of 4 $\mu g \cdot kg^{-1}$ could suppress the hemodynamic response to intubation when a local oropharyngeal anesthetic was given.[9] When associated with propofol 2.4 or 2.5 $mg \cdot kg^{-1}$, fentanyl (2 or 3 $\mu g \cdot kg^{-1}$) decreased the amplitude of the blood pressure response to intubation,[5] and limited the postintubation blood pressure to the baseline value.[3-5] Suppression of the hemodynamic response to intubation could be achieved with a fentanyl dose of 8 $\mu g \cdot kg^{-1}$, given with propofol 1.5 $mg \cdot kg^{-1}$ to premedicated patients.[37]

The original goal of our study was to demonstrate the existence of a statistically significant interaction between fentanyl and propofol. The relation between the doses of drugs and the amplitude of the blood pressure response was not linear. In the statistical analysis of our data, the dose of propofol was indirectly correlated to the hemodynamic response to intubation *via* an interaction, whereas the propofol dose by itself was not significant. The influence of fentanyl seemed predominant and was dose-dependent, predicting that a larger dose of fentanyl given with a smaller dose of propofol could probably abolish the hemodynamic response to intubation, as described by Vermeyen *et al.*[37]

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The heart rate response to intubation could be described by a linear model where the theoretical baseline response to intubation was high (+32 bpm), decreased by the propofol dose (−5.7 × dose in mg/kg) and decreased twice more by fentanyl dose (−10.6 × dose in μg/kg). More surprising was the influence of the product of fentanyl dose and propofol dose (+3.1 × propofol dose × fentanyl dose), which seemed to limit the inhibitor influence of each drug on the heart rate response. Such a model, in which the influence of the association has an opposite sign to the influence of each drug by itself, is one of the simplest that can describe a nonlinear dose–effect relation.

In summary, both postinduction, preintubation and postintubation hemodynamic changes reached a maximal value from a propofol bolus dose of 2 $mg \cdot kg^{-1}$. The addition of fentanyl, 2 or 4 $\mu g \cdot kg^{-1}$ doubled the amplitude of the prestimulation hypotension, but the hypertensive response to intubation was decreased with increasing fentanyl dose. Our data would allow us to make the following suggestions in using propofol and fentanyl for the induction of anesthesia with maximal hemodynamic stability:

- Increasing the dose of propofol to 3.5 $mg \cdot kg^{-1}$ does not alter blood pressure changes before intubation but does not alter the hemodynamic response to intubation.
- Adding fentanyl 2 $\mu g \cdot kg^{-1}$ will decrease hemodynamic response to intubation; administering the fentanyl in close proximity to the initiation of propofol is desirable such that maximal biophase concentration and hypotension would occur at approximately the time of the intubation stimulus.
- In clinical situation where hypertension from intubation is more undesirable than hypotension before intubation, a larger dose of fentanyl (>4 $\mu g \cdot kg^{-1}$) is recommended.

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