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Optimal Propofol–Alfentanil Combinations for Supplementing Nitrous Oxide for Outpatient Surgery

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Background: **The combination of propofol and alfentanil with nitrous oxide provides balanced anesthesia with rapid recovery and minimal emetic side effects. The object of this study was to compare recovery parameters at varying proportions of propofol and alfentanil, and to determine the dosing rate and plasma concentration of propofol necessary to supplement nitrous oxide in the presence of varying concentrations of alfentanil.**

Methods: **Forty-eight patients were anesthetized with nitrous oxide, targeted manual infusions of alfentanil (target plasma concentrations of 0, 50, 100, and 150 ng/ml), and propofol at rates that were varied up or down by 25% depending on the response (movement/no movement) of the preceding patient (at the same alfentanil target concentrations) to ulnar-nerve stimulation. The minimum concentrations of propofol and alfentanil required to prevent movement in 50% of patients (EC_{50}) was determined by logistic regression. Speed of emergence and recovery of cognitive function, time to discharge, and incidence of side effects were compared for four different combinations of propofol and alfentanil with nitrous oxide.**

Results: **The EC_{50} for propofol alone with nitrous oxide was 6.1 μg/ml. Alfentanil, at concentrations of 41 ± 17 (SD), 113 ± 54, and 130 ± 61 ng/ml, reduced the EC_{50} of propofol to 3.3, 2.3, and 2.2 μg/ml, respectively, and decreased emergence time (eye opening) to 8.1, 4.9, and 3.4 min, compared with 24.3 min for propofol alone. Side effects did not differ between groups.**

Conclusions: **The authors conclude that there is a synergistic effect between propofol and alfentanil, and that combining alfentanil with propofol is associated with faster early recovery. (Key words: Cognitive function; emergence; emetic symptoms; recovery.)**

PROPOFOL anesthesia is associated with rapid awakening and a low incidence of postoperative nausea and vomiting.[1,2] It has minimal analgesic effects if administered alone but acts synergistically with opioids to enhance analgesia.[3] Although there has been considerable interest in combinations of propofol with short-acting opioids as part of total intravenous anesthesia, there have been few studies evaluating the effects of combining propofol with a short-acting opioid as a supplement to nitrous oxide. Neither the plasma concentrations nor the dosing rate required for anesthesia have been systematically studied for combinations of alfentanil and propofol with nitrous oxide.

Opioids such as fentanyl and alfentanil have been shown to act synergistically if combined with propofol alone in the absence of nitrous oxide, or if combined with potent inhalational anesthetics.[4,5] Synergy associated with combinations of opioids with inhalational anesthetics exhibits a ceiling effect, whereby increasing opioid concentration beyond some threshold value has a diminishing effect. Opioids may, therefore, alter requirements for propofol in a complex manner. Also, because nitrous oxide is known to have analgesic properties, it is unclear whether propofol-opioid synergy would still exist in the presence of nitrous oxide.[6,7]

The goals of this study were therefore (1) to determine the plasma concentration of propofol required to provide satisfactory anesthesia in the presence of 60% nitrous oxide over a range of alfentanil concentrations, (2) to determine the dosing rates required to achieve adequate anesthesia, and (3) to determine the optimal combination of propofol and alfentanil to supplement ni-

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Table 1. Manual Infusion Scheme for Administering Propofol and Alfentanil

Group	Alfentanil Target	Time Postinduction (min)	Alfentanil Bolus ($\mu g/kg$)	Alfentanil Infusion Rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Propofol Bolus (mg/kg)	Propofol Infusion Rates ($\mu g \cdot kg^{-1} \cdot min^{-1}$)						Median Propofol Rate for Adequate Anesthesia† ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
						−75%	−50%	−25%	0*	+25%	+50%	
A	0	0	0		2							
		0–5		0		0	0	167	356	545	734	377
		5–15		0		95	189	284	379	474	568	403
		15–30		0		74	148	222	296	371	445	315
		30–60		0		58	117	175	233	292	350	292
B	50	0	10		2							
		0–5		0.50		0	0	25	167	309	450	0
		5–15		0.46		71	142	213	284	355	426	178
		15–30		0.40		56	111	167	222	278	334	139
		30–60		0.33		44	87	131	175	219	262	109
C	100	0	19		2							
		0–5		1.01		0	0	0	0	72	167	0
		5–15		0.92		47	95	142	189	237	284	95
		15–30		0.80		37	74	111	148	185	222	74
		30–60		0.67		29	58	87	117	146	175	73
D	150	0	29		2							
		0–5		1.51		0	0	0	0	0	0	0
		5–15		1.38		24	47	71	95	118	142	36
		15–30		1.21		18	37	56	74	93	111	28
		30–60		1.00		15	29	44	58	73	87	29

* Infusion rates for first patient in each group.

† Median rates predicted to provide adequate anesthesia in each treatment group based on response to nerve stimulation at 15 min before surgery, and adequacy of anesthesia at 45 min during surgery (absence of movement or evidence of autonomic stimulation in response to surgery).

trous oxide based on an overall assessment of recovery profiles.

Methods and Materials

This study was performed with approval of the Institutional Review Board at the University of Washington School of Medicine. All patients gave written consent to participation. The subjects studied were 48 adult patients of both sexes undergoing elective ambulatory surgery with general anesthesia. Patients selected for study were 18–65 yr of age, had American Society of Anesthesiologists physical status I or II, and were not taking any medications predicted to alter anesthetic requirements. Thus, patients taking sedatives, anxiolytics, opioids, antidepressants, or anticonvulsants, or who had a recent history of drug or alcohol abuse, were excluded. Also excluded were patients > 20% above ideal body weight.

Patients selected for study were undergoing surgery predicted to last approximately 1–2 h, in which succinylcholine paralysis and oral intubation would be acceptable or indicated.

Patients were randomly assigned to one of four treatment groups, defined by desired target concentrations of alfentanil in plasma as follows: group A = none (n = 12); group B = 50 ng/ml (n = 12); group C = 100 ng/ml (n = 12); group D = 150 ng/ml (n = 12).

All patients completed baseline assessments of nausea, pain, and digit symbol substitution tests before surgery. Patients were then taken to the operating room unpremedicated, with a single intravenous catheter in place. After placement of traditional monitors, and preoxygenation, anesthesia was induced as follows: (1) metubine, 2 mg, 3 min before induction; (2) alfentanil bolus 2 min before induction followed by commencement of a continuous alfentanil infusion; (3) propofol bolus, 2 mg/kg, for induction at time zero; (4) succinylcholine paralysis 1 min after induction, 1.5 mg/kg; (5) intubation 2 min after induction followed by initiation of mechanical ventilation; and (6) administration of 60% nitrous oxide and a continuous infusion of propofol. Continuous infusions of propofol and alfentanil were administered by a Baxter infusion pump using manual infusion schemes shown in table 1 designed to achieve steady-state concentrations of both drugs in plasma. The infusion rates for propofol and alfentanil were based on pharmacokinetic parameters derived from studies of propofol and alfentanil administered to human volunteers.[3] Immediately after in-

duction, a second venous catheter for blood sampling was inserted in the antecubital vein of the arm opposite that used for drug administration.

At 15 min, the response to a noxious stimulus was recorded (movement/no movement). The stimulus consisted of cutaneous stimulation of the ulnar nerve at the wrist using a 40-mA tetanic stimulus at 50 cycles/s applied continuously for 45 s. Subsequently, the response to surgical stimulation (movement/no movement) was also recorded. Cutaneous nerve stimulation always preceded the surgical stimulus. If a subject moved, one or two 50-mg boluses of propofol were administered and the rate of propofol delivery increased by 25%. Additional movement was again treated by repeat bolus and a further 25% increase in rate of propofol infusion.

At 30 min, the rate of propofol delivery was deliberately decreased to obtain a 25% reduction in target concentration, based on observations that anesthetic requirements decrease over time if intubation and incision have been completed. At 45 min, adequacy of anesthesia was again assessed. Inadequate anesthesia was defined as the occurrence of movement, coughing, or bucking in the preceding 15 min, or increase of mean arterial pressure or heart rate by 15% above baseline. Adequate anesthesia was defined as the absence of all of these.

At the end of surgery, delivery of alfentanil and propofol were stopped 15 and 5 min, respectively, before the end of surgery; nitrous oxide was stopped at the end of surgery (last stitch or completion of application of splints). Venous blood samples were obtained before induction; at 10, 15, and 20 min after induction corresponding with the first assessment of anesthetic adequacy; at 40, 45, and 50 min (after reduction of propofol target concentrations at 30 min); at termination of anesthesia (nitrous oxide off); and just before discharge to home.

Recovery Parameters

After termination of nitrous oxide, the length of time required to achieve various milestones of recovery were recorded including the time to eye opening in response to verbal stimulation or light touch, extubation, orientation (to time, place, person), time of transfer from a phase 1 to a phase 2 recovery unit, time to taking fluids orally and ambulation, and time of actual discharge. Patients were extubated when awake and responding to commands, or if coughing or gagging in response to the endotracheal tube. Criteria for transfer to phase 2 included an Aldrete score of 9 or 10, and nausea and vomiting being under control. Discharge criteria from phase 2 to home included stable vital signs; ability to ambulate, take fluids orally, and void; and availability of an escort to take the patient home. Recovery of cognitive function was assessed by serial digit symbol substitution tests administered by a trained technician at 30-min intervals, and performance expressed as a percent of baseline performance (before operation).

Adequacy of ventilation was assessed by measuring oxyhemoglobin saturation while patients breathed room air spontaneously. Room air ventilation was commenced 15 min after recovery-room entry. Saturation $< 92\%$ after 5 min or less was judged to be inadequate and oxygen administered.

Frequency and severity of pain and emetic symptoms were assessed by recording number of vomiting episodes at 30-min intervals until discharge, by visual analogue scale score (0–100 for pain and for nausea, with 0 = no symptoms and 100 = worst possible imaginable pain) provided by patients at 30-min intervals until discharge, and by recording doses of analgesics and antiemetics received before and in the first 24 h after discharge. During the study, nurses were free to administer analgesics and antiemetics when deemed appropriate. Analgesia was provided initially by 25-μg doses of intravenous fentanyl, and subsequently by intravenous or oral nonsteroidal antiinflammatory drugs or oral opioid drugs. Emetic symptoms were treated first with metoclopramide, 10 mg intravenously, and subsequently by ondansetron, 4 mg intravenously, if symptoms persisted.

During the course of study, patients and nurses providing recovery-room care were unaware of what drug combinations or doses the patients had received. All patients were initially taken to phase 1 recovery. One patient was admitted because of hemorrhage that occurred during surgery. All others were discharged on the day of surgery.

All patients received a postoperative phone call within 24–72 h of surgery, at which time they were questioned regarding whether they had side effects of anesthesia (emetic symptoms) or whether they experienced recall of intraoperative events.

Minimum Effective Plasma Concentration of Propofol (EC_{50} and EC_{90})

Within each of groups A–D, the initial dosing rate of propofol (and therefore the target concentration of propofol in plasma in a given patient) was varied up or down in increments of 25% from one patient to the next depending on the response of the previous patient (movement/no movement) to ulnar-nerve stimulation.

Thus, the dosing rate and concentration of propofol in plasma that prevented movement in 50% of patients were bracketed by this technique. The starting target concentration of propofol for the first patient in each group was roughly estimated based on data in the literature relating to use of propofol or alfentanil alone with nitrous oxide.

Modeling of the anesthetic effect after administration of the propofol plus alfentanil combination was performed using the statistical program SYSTAT (version 7.5; SPSS, Chicago, IL). Because the response data were of a binary nature (movement or no movement), logistic regression was used to describe the relationship between the probability of a response to cutaneous nerve stimulation and the average plasma propofol and alfentanil concentrations that were measured between 10 and 15 min. For patients with missing plasma concentration at one of those times, either the 10- or 15-min plasma concentration was used. In 6 of the 48 patients, plasma samples were not available over the 10–15-min period; these patients were excluded from the pharmacodynamic analysis. Response was assigned a value of 1 if the patient failed to move upon cutaneous stimulation and 0 if the patient moved.

If propofol and alfentanil were to act independently (*i.e.*, an additive combination), the logit regression model is described by the following equation. The ratio P(no move)/(1−P(no move)) represents the odds of the patient not moving.

$$\mathrm{Ln}\left(\frac{\mathrm{P(no\ move)}}{1 - \mathrm{P(no\ move)}}\right) = b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf}$$

where P(no move) = the probability of the patient not moving upon noxious stimulation; 1−P(no move) = the probability of the patient moving upon noxious stimulation; C_{prop} = plasma propofol concentration (μg/ml); C_{alf} = plasma alfentanil concentration (ng/ml); b_0, b_1, b_2 = regression coefficients.

If propofol and alfentanil were to modulate each other's action at a common receptor, the logit equation has an extra term that expresses the potential interaction between the two drugs:

$$\mathrm{Ln}\left(\frac{\mathrm{P(no\ move)}}{1 - \mathrm{P(no\ move)}}\right) = b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{prop} \cdot C_{alf}$$

The regression coefficient b_3 for the interaction term could take on either a positive or negative value, depending on whether synergism (supraadditivity) or antagonism (infraadditivity) is observed.

To test for the presence of pharmacodynamic interaction between propofol and alfentanil, the response data were fit to both the additive and interactive logit model equations. The following criteria were used to assess whether the interactive model offered a better fit than the additive model: the visual fit to the data, the overall model fit as indicated by chi-square analysis ($P < 0.05$), the correlation coefficient (r^2), and the significant probability of the interaction term coefficient b_3 being different from zero.

To determine the dosing rates of propofol required to provide satisfactory anesthesia at various rates of alfentanil administration in the presence of nitrous oxide, we determined the median rate of infusion at 10–15 min in responders and nonresponders (movement *vs.* no movement) in each of groups A–D. The point midway between the two medians was assumed to represent the best estimate of the median dosing rate required for adequate anesthesia. Proportional rates of infusion were then calculated for the 15- to 30-min period using the relationship of the median dosing rate given previously to the initial rate of infusion in the first patient in each group. At 30 min, the target concentration and rate of propofol delivery were reduced by 25% and a second assessment of adequacy of anesthesia made at 45 min. Median rates of infusion for adequate *versus* inadequate anesthesia were again determined, and the point midway between the two taken as the median dosing rate required for propofol maintenance from 30–60 min during surgery.

The analysis of propofol was performed on frozen samples of plasma (stored at −20°C), using a gas chromatography–flame ionization detector as described by Yu and Liau[8] using thymol as the internal standard. The mean ± SD was 491 ± 41 ng/ml, and the interday coefficient of variation was 8.4% (< −2% bias) for quality-control samples prespecified to contain 500 ng/ml of propofol. Alfentanil was assayed by a gas chromatography–nitrogen phosphorus detector using the method described by Kintz *et al.*[9] with R38527 (20 ng) as the internal standard. The interday coefficient of variation was 8% (< 2% bias) for samples containing 50 ng/ml alfentanil.

Statistical Analyses

Descriptive statistics were computed by standard techniques. For continuous data, group means were com-

Table 2. Patient Demographics

	Group A (n = 12)	Group B (n = 12)	Group C (n = 12)	Group D (n = 12)
Mean age (yr)	34 ± 10	34 ± 9	35 ± 11	33 ± 10
Mean weight (kg)	71 ± 15	76 ± 20	73 ± 16	71 ± 16
Mean height (cm)	168 ± 8	170 ± 8	165 ± 8	170 ± 8
% males	17	17	17	33
Mean duration of anesthesia (min)	104 ± 44	74 ± 22	78 ± 21	80 ± 30
Type of surgery				
Pelvic laparoscopy	9	7	7	4
Vaginal/perineal	1	2	1	2
Oral/nasal	0	1	0	3
Knee arthroscopy	2	1	2	2
Plastics	0	1	2	1

Values are mean ± SD.

pared by analysis of variance with *post hoc* testing by Bonferroni-Dunn if appropriate. Proportions for categorical data were compared by chi-square analysis. Logistic regression was used to analyze the propofol plus alfentanil plasma concentration-response relationship. An overall $P = 0.05$ was considered significant.

Results

The demographic characteristics of patients studied are shown in table 2. There were no significant differences between groups in age, weight, height, or duration of anesthesia. The mean concentrations of propofol and alfentanil in plasma are shown in figure 1 for groups A-D. Mean plasma concentrations of propofol were not different over the course of 10-, 15-, and 20-min sampling periods within the various groups with the exception of group B, in which plasma concentrations were stable from 10 to 15 min but increased by 20 min compared with the 10-min value. Propofol concentrations for individual patients are shown in figure 2. Similarly, mean alfentanil concentrations were stable from 10-20 min within groups (fig. 1); the individual concentrations are shown in figure 3. In figure 4, the response to nerve stimulation is depicted for all patients in relation to propofol and alfentanil concentrations in plasma. The relationship of propofol and alfentanil plasma concentrations to the response to nerve stimulus were analyzed by logistic regression.

Logistic-regression analysis of the response-concentration data showed that the additive logit model was able to explain the response data with an r^2 value of 0.47 ($P = 0.0003$). Inclusion of an interaction term in the equation improved the fit both statistically and visually ($r^2 = 0.55$, $P = 0.0002$). The regression coefficient of the interaction term (b_3) was positive with a value of 0.0154 ($P = 0.06$), which indicates a synergistic interaction between propofol and alfentanil. To visually judge the fits to the raw data, the logit equations were rearranged to express the plasma propofol concentration that leads to a 50% probability of no movement (EC_{50}) as the dependent variable with the plasma alfentanil concentration as the independent variable (see Appendix). This equation describes a plot that in essence is an isobologram because it represents different combinations of plasma propofol and alfentanil concentrations that yield a 50% probability of no movement. Figure 4 compares such isobolograms for the additive and synergistic models. A good fit of the regression prediction should ideally divide the plotted symbols for patients who did not move and those who did. If the effects were purely additive, one would expect a straight-line relationship. There appears to be a ceiling to the synergistic effect of propofol and alfentanil such that increasing concentrations of alfentanil beyond approximately 100 ng/ml has a diminishing effect on propofol requirements. The equation obtained for the relationship of propofol to alfentanil predicts an anesthetic concentration for alfentanil alone (with nitrous oxide) of 194 ng/ml; similarly, the predicted anesthetic concentration of propofol alone (with nitrous oxide) would be 6.1 μg/ml.

Within each of the treatment groups (A-D), the estimated median infusion rates of propofol required to prevent movement at 15 min or provide adequate anesthesia at 45 min are shown in table 3. These results were used to predict median rates of infusion of propofol required for adequate anesthesia as shown in the last column in table 1.

In table 4, the recovery parameters are shown for all four groups. Early emergence parameters (time to eye

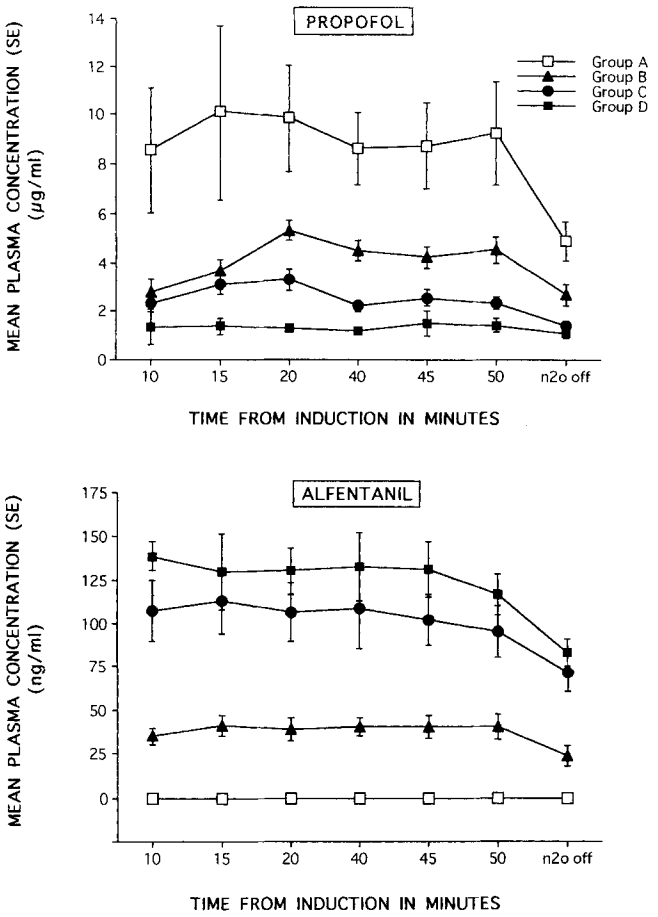

Fig. 1. Mean plasma concentrations of propofol (*top*) and alfentanil (*bottom*) over time in the four treatment groups, A–D. The mean plasma concentrations of alfentanil in the four treatment groups at 15 min (when cutaneous nerve stimulation was applied) were A = 0 ng/ml; B = 41 ± 17 ng/ml; C = 113 ± 54 ng/ml; D = 130 ± 61 ng/ml. The mean plasma concentrations of alfentanil at 45 min when the second assessment of adequate anesthesia was made were 0, 40 ± 17, 102 ± 47, and 131 ± 42 ng/ml. There were no significant changes in concentration over time. Propofol concentrations in plasma were deliberately varied over time in response to patient requirements and reduced by 25% at 30 min. There were no significant differences in mean plasma concentrations from 10–20 min, except in group B, in which the concentration at 20 min (39 ng/ml) was greater than the concentration at 10 min (35 ng/ml), $P = 0.0147$. Similarly, there were no differences in mean plasma concentrations from 40–50 min. Final plasma propofol concentrations (when nitrous oxide was turned off) were 4.9 ± 2.6, 2.7 ± 1.5, 1.4 ± 0.8, and 1.1 ± 0.6 μg/ml. The actual time when nitrous oxide was stopped varied depending on duration of surgery. For graphical reasons, data are presented with ± SE bars in the figure.

opening, extubation, and orientation) were all reduced in a dose-related manner by increasing rates of alfentanil infusion (or plasma concentrations) coupled with decreasing rates of propofol infusion. Oxygen was required at 15 min for oxyhemoglobin desaturation more often in group A compared with the other three groups ($P = 0.01$). Cognitive performance (digit symbol substitution test) improved more rapidly in groups that had received alfentanil (groups B–D) *versus* patients who received no alfentanil (group A). These differences were evident at 30 min but did not persist beyond that time. The times to discharge from phase 1 recovery to phase 2 care were 38 and 29 min less in groups B and C, respectively, compared with group D ($P = 0.0186$ and 0.0018, respectively). The total recovery time (time to discharge) did not differ between groups. Similarly, the incidence and severity of side effects of anesthesia and surgery (pain and emetic symptoms) were not different in the four groups. Despite the fact that 21 of 48 patients moved in response to stimulation at 15 min, none of the patients in any group experienced recall of intraoperative events. Mean drug doses normalized for body weight for patients in this study are shown in table 5.

Discussion

Minimum Effective Plasma Concentration

In this study, regression analysis was used to determine the concentrations of propofol in plasma required to prevent movement in 50% of patients at varying steady-state concentrations of alfentanil in plasma in the presence of inhaled nitrous oxide. In group A, in which patients received propofol but no alfentanil, EC_{50} of propofol with nitrous oxide was 6.1 μg/ml. Alfentanil decreased the requirements for propofol by 46% to 3.3 μg/ml in group B, by 63% to 2.3 μg/ml in group C, and by 64% to 2.2 μg/ml in group D. The results of that analysis suggest there is synergy between propofol and alfentanil, evidenced by the downsloping curve in figure 4. This synergistic effect appeared to plateau if plasma concentrations of alfentanil exceeded 113 ng/ml, similar to what has been described for alfentanil or fentanyl with isoflurane.[5] The synergistic effects that we observed were not abolished by coadministration of nitrous oxide, a known analgesic.

The EC_{50} for propofol alone with nitrous oxide that we obtained (6.1 μg/ml) is higher than reported by Turtle *et al.*[10] (2.5 μg/ml), but patients in the latter study were premedicated with 2–3 mg of lorazepam and received 66% nitrous oxide. Similarly, Spelina *et al.*[11] recorded an EC_{50} of 3.39 μg/ml for propofol with 67% nitrous oxide for skin incision in patients who had received morphine,

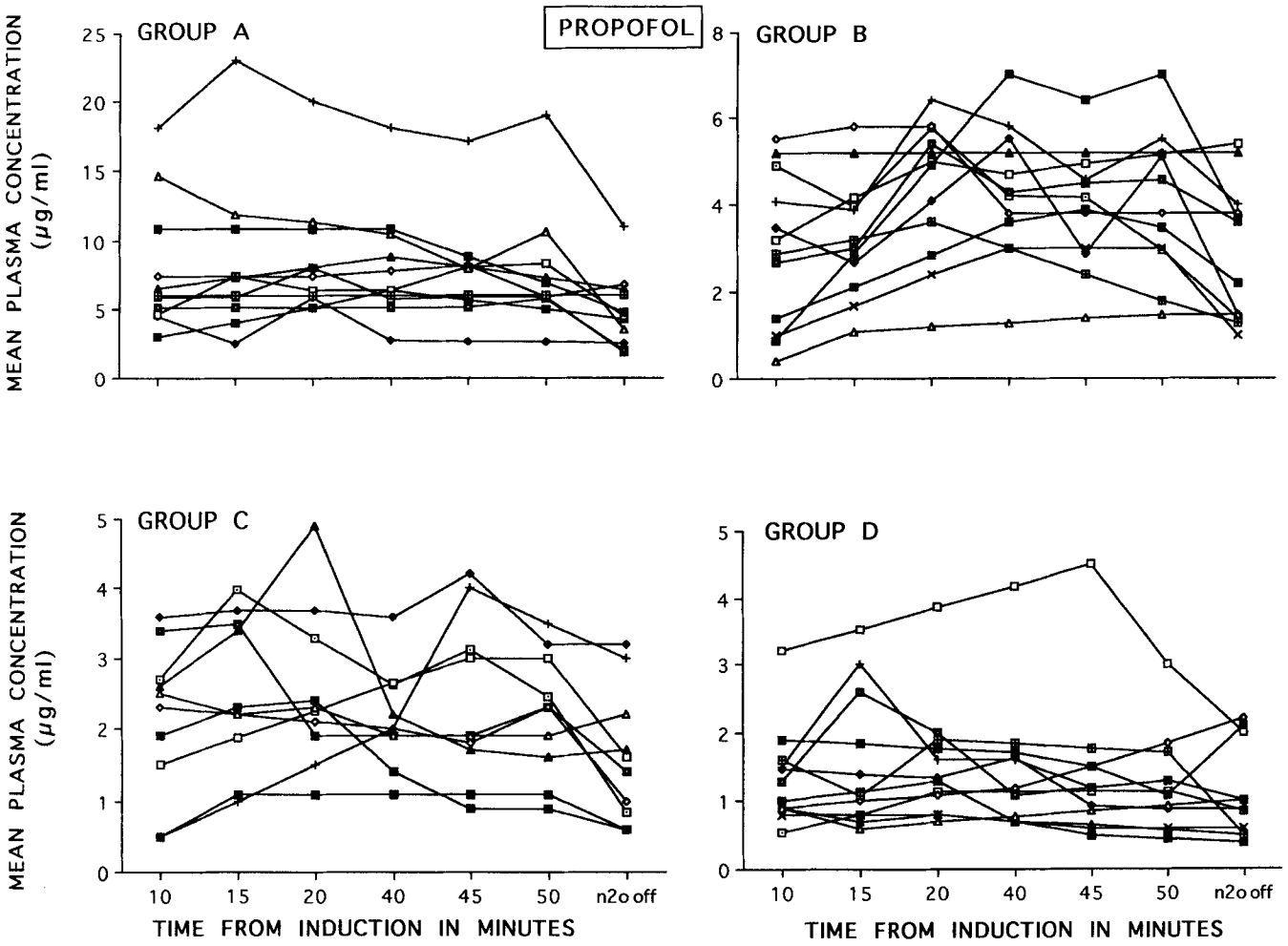

Fig. 2. Individual values for plasma concentrations of propofol during the intraoperative period. For missing values (if blood samples were not obtained), a straight connecting line was drawn to the next measured value. Samples were not obtained if patient movement necessitated bolus administration of propofol within the preceding 10 min.

0.15 mg/kg. Our estimate agrees more closely with the EC_{50} of 5.36 μg/ml reported by Davidson *et al.*[12] for propofol with 67% nitrous oxide in patients premedicated by temazepam. The predicted EC_{50} in our study for alfentanil alone with nitrous oxide (196 ng/ml) is similar to that reported by Ausems *et al.*[13] and by Lemmens *et al.*[14] (279 ng/ml and 226 ng/ml, respectively) for patients receiving 66% nitrous oxide who had been premedicated with benzodiazepines.

Smith *et al.*[15] and more recently Andrews *et al.*[16] have independently reported EC_{50}s for propofol alone (without opioid or nitrous oxide) of 15.2 and 14.3 μg/ml, respectively. This would imply that the 60% nitrous oxide used in our study, constituted approximately 57–60% of an anesthetic, consistent with the observation that the minimum alveolar concentration of nitrous oxide is 1.01 atm (or approximately 100% nitrous oxide), and that such fractions tend to be additive for hypnotic agents.[17,18]

The data obtained in our study are also similar to observations by Vuyk *et al.*[19] concerning the concentrations of propofol and alfentanil required for total intravenous anesthesia in the absence of nitrous oxide.[19] The dose–response curves obtained with their data are similar to ours (fig. 5) but shifted to the right, as might be expected in the absence of nitrous oxide.

Our study can be criticized for use of venous blood samples obtained from an antecubital vein, as opposed to arterial blood samples, for determining plasma concentrations of drugs, because concentrations of drug in

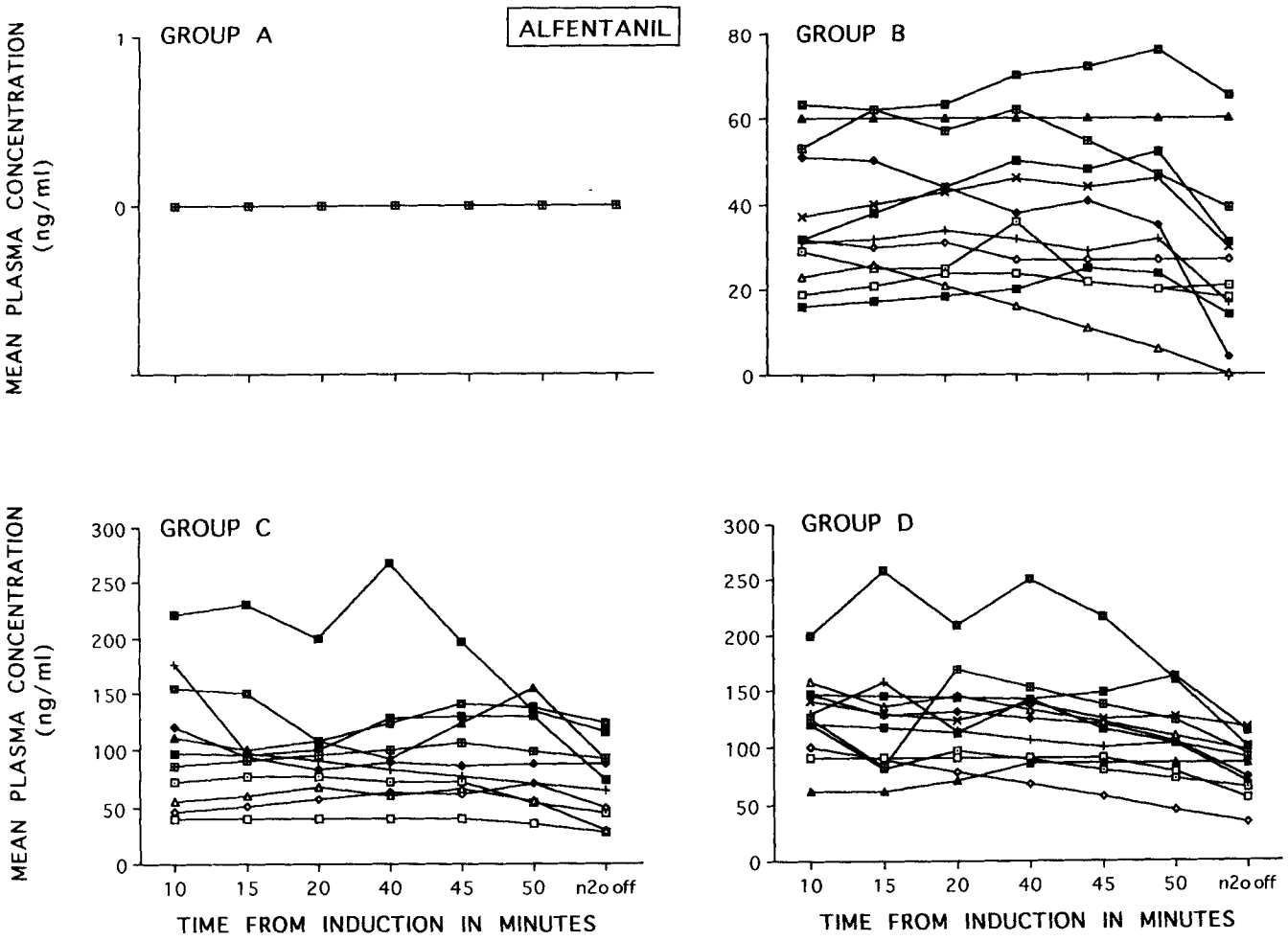

Fig. 3. Individual values for plasma concentrations of alfentanil during the intraoperative period. For missing values (if blood samples were not obtained), a straight connecting line was drawn to the next measured value. Samples were not obtained if patient movement necessitated bolus administration of propofol within the preceding 10 min.

plasma do not necessarily reflect those at effector sites. However, plasma concentrations of drugs were stable over the course of blood sampling at 10, 15, and 20 min, suggesting that a steady state existed (with the possible exception of group B, in which propofol concentrations increased at 20 min). One would expect minimal extraction of drug from the hand or veins in the forearm under these circumstances. Therefore, drug concentrations measured in blood obtained from a radial artery would not be expected to differ significantly from those measured in blood obtained from an antecubital vein. Although we also did not measure blood concentrations at brain effector sites, one would expect equilibration to have occurred by the time the 15-min sample was drawn, particularly because a bolus of propofol was used to induce anesthesia 15 min previously. The reason for the increase of propofol concentration at 20 min in group B is unclear but might be related to pharmacokinetic interaction that has been described if alfentanil is administered simultaneously with propofol.[3]

Median Effective Infusion Rates

There was considerable overlap in the rates of infusion at which patients responded or did not respond to stimulation because of interpatient variability in both the plasma concentrations attained at a given rate of infusion and the plasma concentrations required to provide adequate anesthesia, as well as the relatively small number of patients in each group. We did not therefore use probit analysis or logistic regression for estimating the predicted rates of infusion of propofol for adequate anesthesia. Such an analysis would have extended our

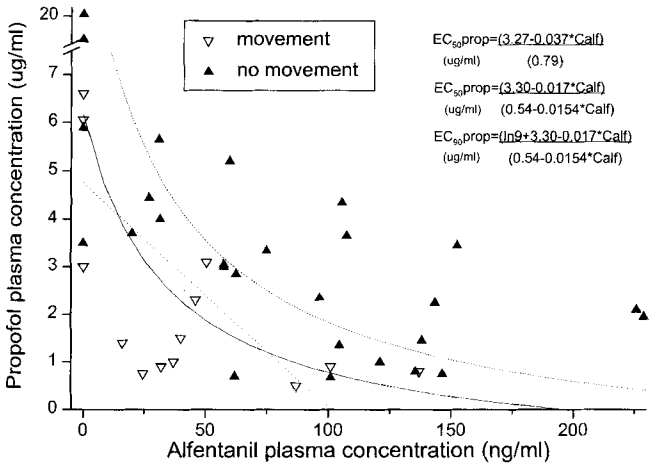

Fig. 4. The propofol–alfentanil concentration isobologram for a 50% probability of no response (movement) to tetanic stimulation of the ulnar nerve at 15 min. The equations obtained by logistic regression for the probability of a response *versus* no response are shown in the figure (solid line = EC_{50}, dashed line = EC_{90}). The EC_{50} for propofol and nitrous oxide alone (without alfentanil) was 6.1 μg/ml. The predicted EC_{50} for alfentanil alone with nitrous oxide (without propofol) was 194 ng/ml. The plasma concentrations utilized in the analysis were those measured in samples taken at 15 min just before nerve stimulation. If both 10- and 15-min samples were obtained, a mean concentration was used for the two samples. If only one sample was obtained (either 10- or 15-min sample), only one value was used in the determination. Blood samples were not obtained at 15 min if patient movement necessitated bolus administration of propofol within the preceding 10 min. The regression obtained assuming additivity (represented by the dotted line) had an R^2 value of 0.47, $P = 0.0003$. The regression obtained by acknowledging propofol–alfentanil interaction (synergy, represented by the solid line) had an R^2 value of 0.55, $P = 0.0002$.

conclusions beyond the precision of our measurements. We chose instead to use a relatively simple approach to describe the relationship between dosing rate and response (adequacy of anesthesia). Specifically, we simply computed median rates of infusion in responders and nonresponders and selected the point midway between the two as the best estimate of the dose rate required to provide adequate anesthesia. This method is somewhat imprecise, and larger numbers of patients would be required to explore these relationships more fully, and provide an assessment of ED_{90} as well as ED_{50}. The medians we have calculated, and the infusion schemes used as shown in table 1, have served in our institution as useful starting points for administering propofol and alfentanil with nitrous oxide and ensuring relatively steady-state concentration of drugs in the plasma. Upward titration of desired targets can conveniently be achieved by bolus administration of propofol (50–100 mg), followed by increasing the infusion rates in table 1 by 25% or 50%. (*i.e.*, by moving one or two columns to the right in table 1). Downward titration of concentration can be achieved by stopping the infusion for 2–3 min, followed by moving one or two columns to the left to decrease the rate of infusion by 25% or 50%. Although computerized administration devices may be simpler to use, they are not readily available to most practitioners.

This study may also be criticized because we used cutaneous nerve stimulation, as opposed to a surgical incision, to estimate anesthetic concentrations or dosing rates necessary to achieve adequate anesthesia. However, Kazama *et al.*[6] and Zbinden *et al.*[20] have demonstrated that results obtained using supramaximal nerve stimulation are similar to those obtained using responses to surgical incision. In our study, all patients, with one exception, failed to respond to surgical stimulus if they had failed to respond to the nerve stimulator. In the one patient who did move, surgical stimulation did not occur for approximately 25 min after nerve stimulation, and plasma concentrations of drugs may have changed in the intervening time.

Table 3. Median Rates of Propofol Infusion to Prevent Movement and Provide Adequate Anesthesia at 15 and 45 Minutes

	Group A	Group B	Group C	Group D
Median rates of propofol infusion at 15 min (μg · kg^{-1} · min^{-1})				
Movers	379	142	95	24
Nonmovers	426	213	95	47
Predicted rate to prevent movement at 15 min in 50% of patients	403	178	95	36
Median rates of infusion at 45 min for adequate anesthesia (μg · kg^{-1} · min^{-1})*				
Not adequate	350	109	73	29
Adequate	233	109	73	29
Predicted rate for adequate anesthesia at 45 min in 50% of patients	292	109	73	29

* Adequate anesthesia was signified by the absence of movement or evidence of autonomic stimulation in response to ongoing surgery.

Table 4. Summary of Recovery Parameters and Side Effects

	Group A	Group B	Group C	Group D
Emergence				
Time to extubation (min)	20.2 ± 13	7.4 ± 5‡	5.2 ± 2‡	3.8 ± 3‡
Time to eye opening (min)	24.3 ± 20	8.1 ± 6‡	4.9 ± 2‡	3.4 ± 3‡
Time to orientation (min)	33.4 ± 21	14.0 ± 7‡	9.9 ± 3‡	6.9 ± 4‡
% intubated on PACU entry	45	0	0	0
% saturation <92% at 15 min	45	17	9	8
Intermediate recovery				
Digit Symbol % control at 30 min	23 ± 29	61 ± 32‡	52 ± 34‡	67 ± 25‡
Time to oral fluids (min)	103 ± 59	63 ± 25	74 ± 32	84 ± 46
Time to ambulation (min)	153 ± 41	111 ± 31	137 ± 52	145 ± 25
Side effects				
Cumulative % vomited	9.1	0	18.2	16.7
Nausea VAS (0–100)*	4 ± 6	7 ± 11	7 ± 14	6 ± 9
Number of antiemetics†	0.4 ± .7	0.9 ± 1.1	0.6 ± 1.0	0.9 ± 1.2
Pain VAS (0–100)*	34 ± 9	19 ± 13	34 ± 23	37 ± 21
Number of fentanyl doses†	2.1 ± 2.3	0.8 ± 1.4	2.5 ± 2.6	2.5 ± 3.4
Number of oral opioid doses†	0.9 ± 1.2	0.9 ± 1.3	1.0 ± 1.1	1.3 ± 1.0
Recovery times				
Phase 1 recovery (min)	87 ± 29	65 ± 20§	74 ± 30§	103 ± 31
Phase 2 recovery (min)	93 ± 33	100 ± 44	109 ± 45	98 ± 42
Total recovery time (min)	179 ± 50	165 ± 54	184 ± 43	201 ± 35

Values are mean ± SD unless otherwise stated.

* Time averaged over the first 120 min of recovery.

† Total number doses/total number patients: fentanyl dose = 25 μg; opioid dose = equivalent to codeine 30 mg.

‡ $P \leq 0.0006$ *versus* group A.

§ $P < 0.0186$–0.0018 *versus* group D.

Recovery Parameters

A primary goal of this study was to compare the recovery characteristics of outpatients anesthetized by propofol in combination with varying doses of alfentanil plus 60% nitrous oxide. The recovery data clearly indicate that emergence time is diminished in a dose-related manner by increasing the rates of alfentanil infusion and simultaneously decreasing the rate of propofol infusion, over the range of doses studied. This effect was still evident at 30 min, at which point depression of cognitive function was less with coutilization of alfentanil compared with propofol alone. However, this difference did not persist, and the duration of phase 1 recovery was shorter in groups B and C as compared with group D, which received the highest dose of alfentanil. Ultimately, the time to discharge to home was not affected. There were also no visible trends with regard to differences in frequency or severity of emetic symptoms or pain. Of interest, the concentrations of propofol attained in the plasma in all of our treatment groups were well above those reported by Gan *et al.*[21] to have antiemetic effects (405 ng/ml, 95% confidence interval of 280–530). At the time of discharge, plasma concentrations of propofol were frequently still at or above the antiemetic threshold

Table 5. Drug Use Computed for the First Hour of Anesthesia Normalized to a 70-kg Patient

	Group A	Group B	Group C	Group D
Propofol dose (mg)				
Induction	140	140	140	140
Maintenance	1,304 ± 373	567 ± 184	387 ± 177	192 ± 111
Total propofol	1,444 ± 373	707 ± 184	527 ± 177	332 ± 111
Alfentanil dose (μg)				
Induction	0	700	1,330	2,030
Maintenance	0	1,553 ± 388	3,199 ± 156	4,288 ± 645
Total alfentanil	0	2,253 ± 388	4529 ± 156	6,318 ± 645

Values are mean ± SD.

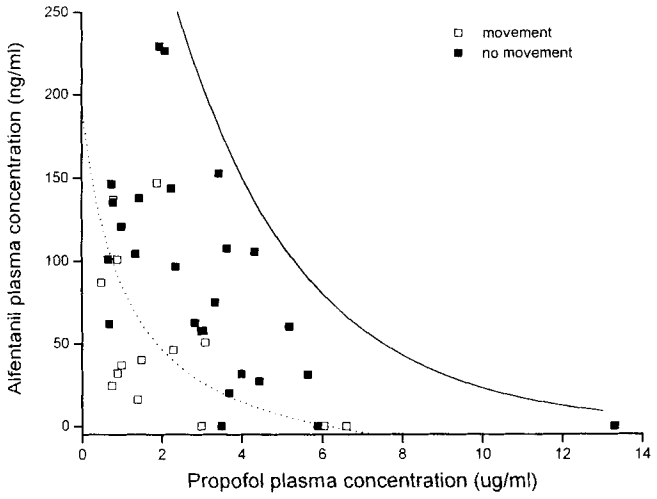

Fig. 5. The propofol–alfentanil concentration isobologram obtained by Vuyk *et al.*[19] for a 50% probability of no response to peritoneal opening using total intravenous anesthesia without nitrous oxide (*solid line*) as compared with the propofol–alfentanil concentration isobologram obtained in our study with nitrous oxide for a 50% probability of no response to cutaneous nerve stimulation (shown as individual data points and a dashed line). There are similar synergistic effects observed. The curve obtained by Vuyk *et al.*[19] is shifted to the right compared with our results, as would be expected in the absence of nitrous oxide. Note that the axes are reversed compared with figure 4.

(means of 689 ng/ml, 456 ng/ml, 237 ng/ml, and 210 ng/ml in groups A–D, respectively), perhaps accounting for the relatively low incidence of nausea and vomiting after discharge (only 1 of 48 patients vomited after discharge). The hourly costs of the B, C, and D protocols were approximately equivalent, and all were less than group A, which received propofol alone. Overall, the data would suggest that the group C protocol may be preferable from the point of view of providing rapid emergence, and recovery of cognitive function, and reducing time required for phase 1 recovery.

In summary, we conclude that

1. The EC_{50} for propofol required to supplement alfentanil and 60% nitrous oxide is given by the equation: EC_{50} prop (μg/ml) = $(3.3 - 0.017 \cdot C_{alf})/(0.54 - 0.0154 \cdot C_{alf})$.
2. Synergy exists between propofol and alfentanil in the presence of nitrous oxide over a range of alfentanil concentrations. This may be of benefit in terms of diminishing drug requirements and costs of anesthesia.
3. Emergence, recovery of cognitive function, and phase 1 discharge are more rapid if propofol is administered in conjunction with alfentanil as opposed to being administered alone as a supplement to nitrous oxide.

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Appendix

To be able to visually judge the data fit, we rearranged the interactive logit model equation to an equation that expressed the probability term P(no move) in terms of C_{prop} and C_{alf} as follows:

$$e^{\text{Ln}\frac{P(\text{no move})}{1-P(\text{no move})}} = e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}}$$

$$\frac{P(\text{no move})}{1 - P(\text{no move})} = e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}}$$

$$P(\text{no move}) = [1 - P(\text{no move})] \cdot e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}}$$

$$P(\text{no move}) + P(\text{no move}) \cdot e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}} = e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}}$$

$$P(\text{no move}) = \frac{e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}}}{1 + e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}}}$$

This equation was further rearranged to enable the construction of a curve that represents all the combinations of plasma alfentanil and propofol concentrations resulting in a 50% probability of keeping the patient from moving, that is, P(no move) = 0.5. That is,

$$0.5 = \frac{e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}}}{1 + e^{b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{alf} \cdot C_{prop}}}$$

Therefore,

$$b_0 + b_1 \cdot C_{prop} + b_2 \cdot C_{alf} + b_3 \cdot C_{prop} \cdot C_{alf} = 0$$

$$b_1 \cdot C_{prop} + b_3 \cdot C_{prop} \cdot C_{alf} = -b_0 - b_2 \cdot C_{alf}$$

$$C_{prop} \cdot (b_1 + b_3 \cdot C_{alf}) = -b_0 - b_2 \cdot C_{alf}$$

$$C_{prop} = \frac{-b_0 - b_2 \cdot C_{alf}}{b_1 + b_3 \cdot C_{alf}}$$

Because this equation applies to a prespecified probability level of 0.5, the concentration variable C_{prop} is redefined as EC_{50}^{prop}; that is, a plasma concentration of propofol needed to achieve a 50% probability that the patient would fail to move upon cutaneous stimulation at a preexisting concentration of alfentanil (C_{alf}).

$$EC_{50}^{prop} = \frac{-b_0 - b_2 \cdot C_{alf}}{b_1 + b_3 \cdot C_{alf}}$$

A similar procedure was followed to simulate a curve that represents all the combinations of alfentanil and propofol that have a 90% probability of keeping the patient from moving, that is, P(no move) = 0.9:

$$EC_{90}^{prop} = \frac{\ln 9 - b_0 - b_2 \cdot C_{alf}}{b_1 + b_3 \cdot C_{alf}}$$