

Anesthesiology  
1996; 84:288-99  
© 1996 American Society of Anesthesiologists, Inc.  
Lippincott-Raven Publishers

## Pharmacodynamic Interaction between Propofol and Alfentanil When Given for Induction of Anesthesia

Jaap Vuyk, M.D., Ph.D.,\* Frank H. M. Engbers, M.D.,\* Anton G. L. Burm, M.Sc., Ph.D.,† Arie A. Vletter, B.Sc.,‡ Gerard E. R. Griever, M.D.,§ Erik Olofson, M.Sc.,|| James G. Bovill, M.D., Ph.D., F.F.A.R.C.S.I.#

**Background:** Propofol and alfentanil often are combined during induction of anesthesia. However, the interaction between these agents during induction has not been studied in detail. The influence of alfentanil on the propofol concentration-effect relationships was studied for loss of eyelash reflex, loss of consciousness, and hemodynamic function in 20 unpremedicated ASA physical status 1 patients aged 20-55 yr.

**Methods:** Patients were randomly divided into four groups to receive a computer-controlled infusion of alfentanil with target concentrations of 0, 50, 200, or 400 ng/ml (groups A, B, C, and D, respectively). While the target concentration of alfentanil was maintained constant, patients received a computer-controlled infusion of propofol, with an initial target concentration of 0.5-1 µg/ml, that was increased every 12 min by 0.5-1 µg/ml. Every 3 min, the eyelash reflex and state of consciousness were tested and an arterial blood sample was taken for blood propofol and plasma alfentanil determination. The propofol-alfentanil concentration-response relationships for loss of eyelash reflex and loss of consciousness were determined by nonlinear regression, and for the percentage of change in systolic blood pressure and heart rate by logistic regression.

**Results:** The patient characteristics did not differ significantly among the four groups. The patients in groups A and B continued to breathe adequately, whereas all patients in groups C and D required assisted ventilation. End-tidal carbon dioxide partial pressure remained less than 46 mmHg in all

patients. With plasma alfentanil concentrations increasing from 0 to 500 ng/ml, the  $EC_{50}$  of propofol decreased from 2.07 to 0.83 µg/ml for loss of eyelash reflex and from 3.62 to 1.55 µg/ml for loss of consciousness. With plasma alfentanil concentrations increasing from 0 to 500 ng/ml, the blood propofol concentrations associated with a 10% decrease in systolic blood pressure and heart rate decreased from 1.68 to 0.17 µg/ml and from 2.36 to 0.04 µg/ml, respectively.

**Conclusions:** Alfentanil significantly reduces blood propofol concentrations required for loss of eyelash reflex and loss of consciousness. In addition, alfentanil enhances the depressant effects of propofol on systolic blood pressure and heart rate. Hemodynamic stability, therefore, does not increase in patients receiving propofol in combination with alfentanil compared to those receiving propofol as the sole agent for induction of anesthesia. (Key words: Anesthetic techniques, intravenous: computer-controlled infusion. Anesthetics, intravenous: alfentanil; propofol. Pharmacodynamics: alfentanil; drug-drug interactions; propofol.)

DRUG interactions can be either beneficial or detrimental to the patient receiving a combination of drugs. Because of their clinical importance, adverse drug interactions frequently are reported and have been well documented.<sup>1</sup> To date, beneficial drug interactions have received less attention. In anesthetic practice, however, wide use is made of such drug interactions. For most inhalational and intravenous anesthetics, the administration of drug combinations reduces the dose requirements of the individual agents.<sup>2-7</sup> Furthermore, the magnitude of various side effects (the reduction of hemodynamic or ventilatory function) generally is considered to be less when the drugs are combined than when they are given alone to obtain a specific therapeutic effect. However, to date, scientific data supporting this theory are scarce.

Recently, we have shown that 50% of female patients lost consciousness at a blood propofol concentration of 3.4 µg/ml.<sup>8</sup> Furthermore, we have described the interaction between propofol and alfentanil for the suppression of responses to lower abdominal surgical stimuli.<sup>9</sup> Propofol markedly reduced the alfentanil

\* Staff Anesthesiologist.

† Associate Professor of Anesthesiology.

‡ Laboratory Technician.

§ Research Assistant.

|| Research Associate.

# Professor of Anesthesiology.

Received from the Department of Anaesthesiology, University Hospital Leiden, Leiden, The Netherlands. Submitted for publication March 3, 1995. Accepted for publication October 14, 1995. Presented at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 17, 1994. Supported in part by ZENECA-Farma, Ridderkerk, The Netherlands.

Address reprint requests to Dr. Vuyk: Department of Anaesthesiology, University Hospital Leiden, P.O. Box 9600, 2300 RC Leiden, The Netherlands.

concentrations required for responses to perioperative stimuli in combination with short and coworkers<sup>6</sup> receive dose requirements for hypnosis by concomitant administration of propofol concentrations were blood-effect site equilibrium consideration. The importance of fibrillation as a determinant has been stressed recently the propofol-alfentanil interaction of consciousness thus remains the magnitude of various side effects of propofol and alfentanil dynamic function) a combination of therapeutic effects (e.g., yet unknown.

This study examined the propofol and alfentanil for loss of consciousness in patients undergoing general surgery. In addition, we examined the changes in the arterial blood pressure and heart rate generated by propofol and alfentanil at concentrations that caused loss of consciousness.

### Materials and Methods

With approval of the local ethics committee and informed consent of the patients, 20 ASA physical status 1 who were aged 20-55 yr, had no known cardiac, pulmonary, or renal disease, and patients receiving no premedication or sedatives, were excluded from the study. Patients consuming more than 20 cigarettes per day were randomly divided into four groups (groups A, B, C, and D) to receive alfentanil by computer-controlled infusion at a target concentration of 0, 50, 200, or 400 ng/ml (groups A, B, C, and D). The computer-controlled infusion was performed using an Atari Portfolio pocket computer (Apple Computer, Japan) coupled to an Ohmeda

"Schüttler L. Schwilden H. St. modelling of diprivan (abstract)

## PHARMACODYNAMIC INTERACTION OF PROPOFOL AND ALFENTANIL

concentrations required for the suppression of responses to perioperative stimuli, and acted synergistically in combination with alfentanil in this respect.<sup>9</sup> Short and coworkers<sup>6</sup> recently reported that propofol dose requirements for hypnosis were reduced up to 80% by concomitant administration of alfentanil. In that study, however, plasma alfentanil or blood propofol concentrations were not measured, whereas blood-effect site equilibration was not taken into consideration. The importance of blood-effect site equilibration as a determinant of induction dose requirements has been stressed recently.<sup>10</sup> The true nature of the propofol-alfentanil interaction for sedation or loss of consciousness thus remains uncertain. Furthermore, the magnitude of various side effects of the combination of propofol and alfentanil (e.g., reduction in hemodynamic function) at concentrations associated with therapeutic effects (e.g., loss of consciousness) is as yet unknown.

This study examined the interaction between propofol and alfentanil for loss of eyelash reflex and loss of consciousness in patients scheduled to undergo general surgery. In addition, we investigated the magnitude of the changes in the arterial systolic blood pressure and heart rate generated by the combination of propofol and alfentanil at concentrations associated with loss of consciousness.

### Materials and Methods

With approval of the local Medical Ethics Committee and informed consent of patients, 20 patients of ASA physical status 1 who were scheduled for general surgery and aged 20–55 yr, participated in the study. Patients with known cardiac, pulmonary, or renal disease, and patients receiving medication, including oral contraceptives, were excluded from the study. Patients consuming more than 20 g of alcohol or smoking more than 10 cigarettes per day were also excluded.<sup>11</sup> Patients were randomly divided into four groups to receive alfentanil by computer-controlled infusion at a target concentration of either 0, 50, 200, or 400 ng/ml (groups A, B, C, and D, respectively).

The computer-controlled infusion system consisted of an Atari Portfolio pocket computer (Atari, Okasaki, Japan) coupled to an Ohmeda 9000 infusion pump.

The system was supplied with two-compartment pharmacokinetic data<sup>12</sup> of propofol. A second system, supplied with three-compartment population-based pharmacokinetic data of alfentanil,<sup>13</sup> adjusted for patient gender, weight, and age, was used to administer alfentanil. No preanesthetic medication was administered.

In the operating room, an intravenous cannula was inserted into a large forearm vein for the infusion of propofol and alfentanil, and another cannula was inserted in a radial artery for continuous measurement of arterial blood pressure and collection of blood samples for propofol and alfentanil determination. The electrocardiogram, arterial blood pressure, heart rate, end-tidal carbon dioxide partial pressure, and oxyhemoglobin saturation (Nellcor N-200, Hayward, CA) were monitored continuously throughout the study.

With the patients breathing 30% oxygen in air, the alfentanil infusion was started at a target concentration of either 0, 50, 200, or 400 ng/ml in the patients in groups A, B, C, and D, respectively. This target alfentanil concentration was maintained constant throughout the study. At the same time, the propofol infusion was started at a target propofol concentration of 0.5–1 µg/ml. The target propofol concentration was increased every 12 min (4 times the blood-effect site equilibration half-life of propofol)<sup>12</sup> by 0.5–1 µg/ml, depending on the degree of sedation, until a sufficient number of hemodynamic data had been obtained, and the patients had lost consciousness.

Every 3 min, the eyelash reflex was tested and the patients were asked to open their eyes or to otherwise indicate that they were still conscious. If no response to these stimuli occurred, the patients were stimulated manually by gently rubbing their shoulders and the response was noted. Loss of consciousness was defined as unresponsiveness to both verbal and tactile stimuli.

Throughout the study, patients were observed for inadequate ventilation. Inadequate ventilation was defined as an end-tidal carbon dioxide partial pressure exceeding 46 mmHg, and/or an oxyhemoglobin saturation of less than 90%. When the patients breathed inadequately, the ventilation was assisted with a mask and bag to maintain the end-tidal carbon dioxide partial pressure below 46 mmHg, and the oxyhemoglobin saturation greater than 90%. When loss of consciousness was induced and an adequate number of hemodynamic data had been obtained, the study was terminated, 1 mg/kg was succinylcholine was administered, the trachea of the patient was intubated, and anesthesia was continued with the computer-controlled infusion of

<sup>12</sup> Schüttler L, Schwilden H, Stoessel H: Pharmacokinetic-dynamic modelling of diprivan (abstract). *ANESTHESIOLOGY* 1986; 65:A549.

propofol and alfentanil. Twenty-four hours postoperatively, the patients were queried as to their recollection of events during the study period and intubation.

#### Blood Samples and Assays

Arterial blood samples for determination of the whole blood propofol concentration were taken just before the start of the propofol infusion and every 3 min thereafter until the trachea was intubated. Blood samples were transferred into test tubes containing potassium oxalate and stored at 4°C. Assays were carried out within 12 weeks. Propofol concentrations in blood were measured by reversed-phase high-performance liquid chromatography.<sup>8</sup> The detection limit was approximately 5 ng propofol per milliliter of blood. The coefficient of variation of the high-performance liquid chromatographic method did not exceed 7% in the concentration range encountered in this study.

Every 3–6 min, an additional blood sample was taken in a heparinized syringe for determination of the plasma alfentanil concentration. The concentrations of alfentanil in plasma were determined by capillary gas chromatography.<sup>14</sup> The detection limit was approximately 0.2 ng alfentanil per milliliter of plasma. The coefficient of variation of the gas chromatographic method did not exceed 5% in the concentration range encountered in this study.

#### Data Analysis

The patient characteristics were compared between the patients of the four groups using one-way analysis of variance followed by the student Newman-Keuls test, if appropriate.

The interaction between propofol and alfentanil for loss of eyelash reflex and loss of consciousness was determined by nonlinear regression analysis. For each patient, the mid-range propofol and mid-range alfentanil concentrations were calculated between the measured concentrations at the time of loss of eyelash reflex and the measured concentrations at the time when the patient still responded to the testing of the eyelash reflex at the previous target propofol step. Similarly, these mid-range propofol and alfentanil concentrations were calculated for loss of consciousness. The mid-range propofol concentrations determined for loss of eyelash reflex and loss of consciousness in the individual patients were then related to the corresponding mid-range plasma alfentanil concentrations by an unweighted least-squares nonlinear regression analysis over all patients ( $n = 19$ , see Appendix). For both endpoints,

both the possibilities of an additive, and nonadditive interaction were explored. The residual sum of squares of both fitted curves of each endpoint were compared with an F-test (Appendix). The nature of the interaction between propofol and alfentanil for loss of eyelash reflex and loss of consciousness was then determined using the isobolographic method.<sup>15</sup>

The effect of propofol and alfentanil on hemodynamic function was characterized by deriving the propofol and alfentanil concentration combinations that caused a 10%, 20%, and 30% decrease in the arterial systolic blood pressure and heart rate using logistic regression (Appendix). Immediate preinduction arterial systolic blood pressure and heart rate values were used as control data. For the three curves of both hemodynamic parameters, both the possibilities of an additive, and nonadditive interaction were explored. The logistic regression that demonstrated the highest correlation with the raw data, was considered to represent the best fitted line.<sup>16</sup> Furthermore, the decrease in the systolic blood pressure and heart rate values that occurred at loss of consciousness in the individual patients were compared between the patients in the four groups using one-way analysis of variance followed by a Tukey test, if appropriate.

Performance of the computer-controlled infusion systems of propofol and alfentanil was evaluated as follows. For each blood sample, the performance error was calculated as  $((C_m - C_p)/C_p) \times 100$ , where  $C_m$  and  $C_p$  are the measured and predicted blood propofol or plasma alfentanil concentrations.<sup>17–19</sup> Subsequently, the bias and inaccuracy of each system were assessed by determination of the median performance error and the absolute performance error (MDAPE), and the corresponding 95% confidence intervals. When the 95% confidence interval of the median performance error included zero, it was concluded that no significant bias had occurred. In addition, the effect of time on the performance error was evaluated by linear regression.

Data are presented as mean  $\pm$  SD, median and range, or as a percentage, unless stated otherwise.  $P < 0.05$  was considered as the minimum level of statistical significance.

#### Results

The age, weight, and sex distribution did not differ among the patients of the four groups (table 1). None of the patients experienced rigidity during the study period, or reported awareness during intubation. The

Table 1. Characteristics of the Patients in Groups A, B, C, and D, Receiving Propofol in a Concentration of 0 (Group A) or 400 ng/ml (Group D)

	Group A	Group B	Group C	Group D
n	5	5	5	5
Age (yr)	35 $\pm$ 6	35 $\pm$ 6	35 $\pm$ 6	35 $\pm$ 6
Weight (kg)	62 $\pm$ 5	62 $\pm$ 5	62 $\pm$ 5	62 $\pm$ 5
Sex (F/M)	4/1	4/1	4/1	4/1

patients in groups A and B received propofol with assistance throughout the procedure. In groups C and D already at the lowest target propofol concentration (0.25  $\mu$ g/ml) tidal carbon dioxide partial pressure was 46 mmHg in all patients. Loss of consciousness when propofol concentration was increased to 2.07  $\mu$ g/ml. Measured plasma alfentanil concentration was 0.2 ng/ml (target alfentanil concentration was 0.2 ng/ml). In the patient, in whom juvenile myoclonic epilepsy developed 4 yr previously, a steroid anti-inflammatory was given until 7 days before surgery. This patient was not included in the study. The plasma alfentanil concentration was stable over time in all patients. Measured blood propofol concentration decreased in a stepwise fashion (fig. 2). At the target propofol concentration of 0.25  $\mu$ g/ml, the blood propofol concentration reduced the blood propofol concentration with loss of eyelash reflex. With plasma alfentanil concentration of 0.2 ng/ml, the propofol concentration with loss of eyelash reflex decreased from 2.07 to 0.83  $\mu$ g/ml. The relationship associated with loss of consciousness decreased from 2.07 and 4 (table 2). Both the relationship for loss of eyelash reflex and loss of consciousness were best characterized by the isobole (Appendix). In figures 5 and 6, the relationship between blood pressure and heart rate and alfentanil with respect to propofol concentration by alfentanil concentration on hemodynamic function. The propofol concentrations increased with the propofol concentration.

## PHARMACODYNAMIC INTERACTION OF PROPOFOL AND ALFENTANIL

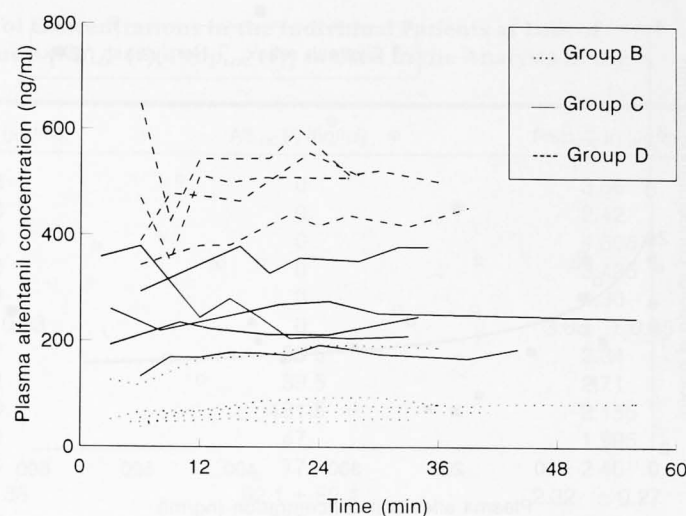
**Table 1. Characteristics of the Patients of Groups A–D, Receiving Propofol in Addition to a Target Alfentanil Concentration of 0 (Group A), 50 (Group B), 200 (Group C), or 400 ng/ml (Group D)**

	Group A	Group B	Group C	Group D
n	5	5	5	4
Age (yr)	35 ± 6	29 ± 5	35 ± 5	40 ± 10
Weight (kg)	62 ± 5	77 ± 15	82 ± 11	67 ± 11
Sex (F/M)	4/1	2/3	3/2	3/1

patients in groups A and B breathed adequately without assistance throughout the study, whereas all patients in groups C and D already required assisted ventilation at the lowest target propofol concentration. The end-tidal carbon dioxide partial pressure remained less than 46 mmHg in all patients. One patient from group D lost consciousness when the blood propofol concentration was increased to 2.56  $\mu\text{g/ml}$  with a mean measured plasma alfentanil concentration of 868 ng/ml (target alfentanil concentration: 400 ng/ml). This male patient, in whom juvenile rheumatoid arthritis had developed 4 yr previously, and who had been taking non-steroidal anti-inflammatory medication on a daily basis until 7 days before surgery, was a distinct outlier and was not included in the data analysis.

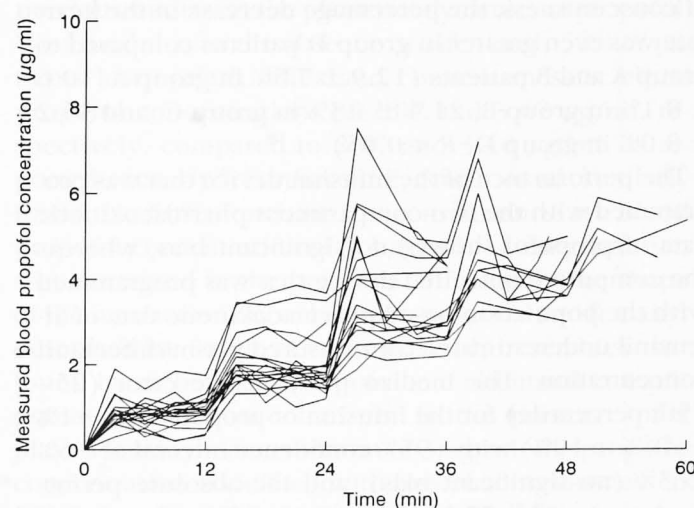
The plasma alfentanil concentrations remained fairly stable over time in all patients (fig. 1), while the measured blood propofol concentrations increased in a stepwise fashion (fig. 2) corresponding closely with target propofol concentrations. Alfentanil significantly reduced the blood propofol concentration associated with loss of eyelash reflex and loss of consciousness. With plasma alfentanil concentrations increasing from 0 to 500 ng/ml, the propofol concentration associated with loss of eyelash reflex in 50% of patients decreased from 2.07 to 0.83  $\mu\text{g/ml}$ , and the propofol concentration associated with loss of consciousness in 50% of patients decreased from 3.62 to 1.55  $\mu\text{g/ml}$  (figs. 3 and 4 and table 2). Both the concentration-effect relationship for loss of eyelash reflex and for loss of consciousness were best characterized by a concave-up isobole (Appendix).

In figures 5 and 6, the interaction between propofol and alfentanil with respect to reduction in the systolic blood pressure and heart rate is shown. The supplementation by alfentanil enhanced the effects of propofol on hemodynamic function. With plasma alfentanil concentrations increasing from 0 to 500 ng/ml, the propofol concentration associated with a 10% de-



**Fig. 1. The measured plasma alfentanil concentrations versus time of the 14 patients who received a computer-controlled infusion of alfentanil with a constant target concentration of 50, 200, or 400 ng/ml.**

crease in the systolic blood pressure in 50% of patients decreased from 1.68 to 0.17  $\mu\text{g/ml}$ , and the propofol concentration associated with a 10% decrease in the heart rate in 50% of patients decreased from 2.36 to 0.04  $\mu\text{g/ml}$ . The supplementation by alfentanil, although reducing propofol requirements, did not increase the hemodynamic stability during induction of anesthesia. At loss of consciousness, no significant difference was found in the percentage decrease in the



**Fig. 2. The measured blood propofol concentrations versus time of the 19 patients who received a computer controlled infusion of propofol with a target concentration that was increased every 12 min with 0.5–1  $\mu\text{g/ml}$ .**

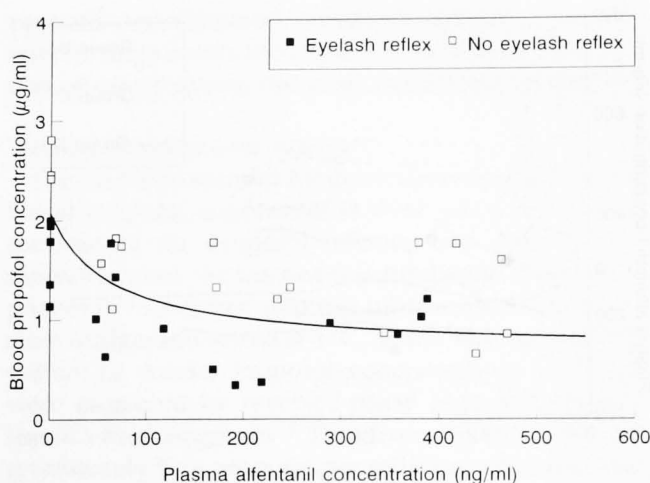


Fig. 3. The concentration-effect relationship of the combination of propofol and alfentanil for loss of eyelash reflex. The open squares represent the highest blood propofol and plasma alfentanil concentrations associated with the presence of the eyelash reflex. The filled squares represent the blood propofol and plasma alfentanil concentrations associated with the loss of eyelash reflex. The curve represents alfentanil and propofol concentrations associated with a 50% probability of loss of eyelash reflex and is described by the equation: mid-range propofol =  $(2067.969 * (-198.56 - C_{Alf})) / (-198.56 - 3.08183 * C_{Alf})$ ,  $R^2 = 0.68$ . The curve runs asymptotically to a horizontal line defined as  $C_{prop} = 0.67 \mu\text{g/ml}$ , suggesting that loss of eyelash reflex does not occur below this blood propofol concentration, regardless how high the plasma alfentanil concentration.

systolic blood pressure between the groups ( $22.7 \pm 4.5\%$  in group A,  $29.6 \pm 10.7\%$  in group B,  $24.7 \pm 5.5\%$  in group C, and  $27.0 \pm 6.2\%$  in group D). At loss of consciousness, the percentage decrease in the heart rate was even greater in group D patients compared to group A and B patients ( $12.9 \pm 7.5\%$  in group A,  $10.6 \pm 8.1\%$  in group B,  $21.4 \pm 4.3\%$  in group C, and  $35.2 \pm 8.0\%$  in group D,  $P < 0.05$ ).

The performance of the infusion device that was programmed with the two-compartment pharmacokinetic data of propofol showed no significant bias, whereas the computer-controlled device that was programmed with the population-based pharmacokinetic data of alfentanil underestimated the measured plasma alfentanil concentration. The median performance error (25–75th percentile) for the infusion of propofol was  $-1\%$  ( $-14\%$  to  $19\%$ ) with a 95% confidence interval of  $-6\%$  to  $3\%$  (no significant bias), and the absolute performance error (25–75th) was  $16\%$  ( $8\%$ – $28\%$ ). The median performance error (25–75th) for the infusion of alfentanil was  $23\%$  ( $-4\%$  to  $48\%$ ) with a 95% confidence interval of  $13\%$ – $29\%$ , and the absolute performance error

(25–75th) was  $26\%$  ( $11\%$ – $48\%$ ). The performance error of the propofol and alfentanil infusion systems did not change over time.

## Discussion

The objective of this investigation was to characterize the interaction between propofol and alfentanil both for therapeutic and side effects when given to induce anesthesia. To evaluate whether a combination of agents is preferable to the agents individually, it is necessary to characterize the interaction between these agents with respect to the therapeutic effects as well as to the side effects. In general, when a combination shows a more powerful interaction with respect to a therapeutic effect, compared to the interaction with respect to the side effects (e.g., therapeutic effects: synergistic *vs.* side effects: additive; or therapeutic effects: additive *vs.* side effects: infraadditive), the use of the combination is to be preferred to the administration of the individual agents. When the reverse holds

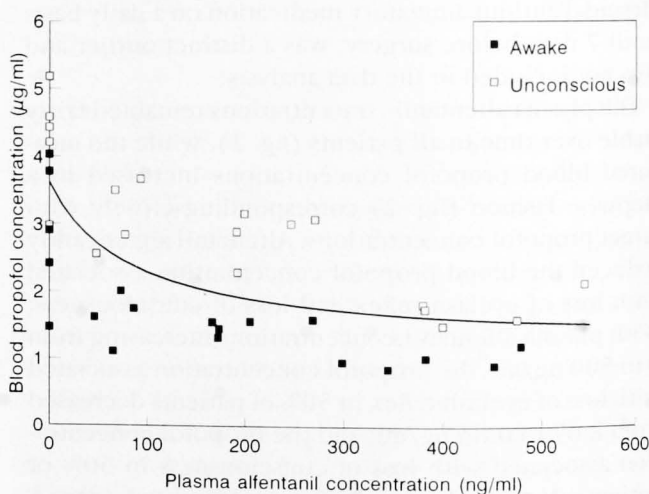


Fig. 4. The concentration-effect relationship of the combination of propofol and alfentanil for loss of consciousness. The open squares represent the highest blood propofol and plasma alfentanil concentrations associated at which patients still were conscious. The filled squares represent the blood propofol and plasma alfentanil concentrations associated with loss of consciousness. The curve represents alfentanil and propofol concentrations associated with a 50% probability of loss of consciousness and is described by the equation: loss of consciousness =  $(3620.003 * (-240.377 - C_{Alf})) / (-240.377 - 2.98379 * C_{Alf})$ ,  $R^2 = 0.72$ . The curve runs asymptotically to a horizontal line defined as  $C_{prop} = 1.21 \mu\text{g/ml}$ , suggesting that loss of consciousness does not occur below this blood propofol concentration, regardless how high the plasma alfentanil concentration.

Table 2. Midrange Plasma Alfentanil Concentration (Alf<sub>LOER</sub>) (i), Propofol Concentration (Prop<sub>LOER</sub>) (i), and Patients of the Four Groups

Patient No.	Alf <sub>LOER</sub> (i)	Prop <sub>LOER</sub> (i)
A1		
A2		
A3		
A4		
A5		
Mean ± SD		
B1		
B2		
B3		
B4		
B5		
Mean ± SD		
C1		
C2		
C3		
C4		
C5		
Mean ± SD		
D1		
D2		
D3		
D4		
Mean ± SD		

true (an infraadditive interaction) for therapeutic effects, an additive interaction with respect to the combination generally would be expected. In view of this, we studied the interaction of propofol and alfentanil both for therapeutic effects and side effects, i.e., change in consciousness. To evaluate whether the combination of propofol and alfentanil is beneficial or not, we studied this regard during induction of anesthesia. With the use of two-compartment infusion devices, we were able to study the interaction of propofol and alfentanil at concentrations that, after an appropriate adjustment, required for blood-effect site concentrations to correspond closely in the biophase. With the use of the pharmacokinetic data of propofol and alfentanil, the computer-controlled infusion of propofol and plasma alfentanil concentrations obtained (figs. 1 and 2). The concentrations closely corresponded to those obtained by the computer-controlled

## PHARMACODYNAMIC INTERACTION OF PROPOFOL AND ALFENTANIL

Table 2. Midrange Plasma Alfentanil and Midrange Blood Propofol Concentrations in the Individual Patients at Loss of Eyelash Reflex [ $Alf_{LOER}(i)$ ,  $Prop_{LOER}(i)$ ] and at Loss of Consciousness [ $Alf_{LOC}(i)$ ,  $Prop_{LOC}(i)$ ] as Used in the Analysis in the Patients of the Four Groups

Patient No.	$Alf_{LOER}(i)$ (ng/ml)	$Prop_{LOER}(i)$ ( $\mu$ g/ml)	$Alf_{LOC}(i)$ (ng/ml)	$Prop_{LOC}(i)$ ( $\mu$ g/ml)
A1	0	2.38	0	3.56
A2	0	1.68	0	2.42
A3	0	2.40	0	4.605
A4	0	1.78	0	3.425
A5	0	2.13	0	4.30
Mean $\pm$ SD	0	2.07 $\pm$ 0.33	0	3.66 $\pm$ 0.85
B1	62	0.87	65.5	2.34
B2	68	1.62	89.5	2.71
B3	145	1.20	181.5	2.155
B4	50	1.29	47	1.995
B5	79	1.76	77	2.40
Mean $\pm$ SD	80.8 $\pm$ 37.4	1.35 $\pm$ 0.35	92.1 $\pm$ 52.4	2.32 $\pm$ 0.27
C1	233	0.85	269	2.12
C2	213	0.77	203	2.40
C3	360	0.90	229	2.37
C4	169	1.13	182.5	1.87
C5	344	0.43	361.5	1.36
Mean $\pm$ SD	236.8 $\pm$ 84.0	0.82 $\pm$ 0.25	249.0 $\pm$ 70.7	2.02 $\pm$ 0.43
D1	470	0.42	484.5	1.22
D2	358	1.37	362	1.355
D3	410	0.80	463	1.57
D4	424	1.39	476	1.395
Mean $\pm$ SD	415.5 $\pm$ 46.1	0.995 $\pm$ 0.47	446.6 $\pm$ 56.9	1.385 $\pm$ 0.14

true (an infraadditive interaction with respect to the therapeutic effects, an additive or supraadditive interaction with respect to the side effects), the use of the combination generally will be disadvantageous.<sup>15</sup> In view of this, we studied the interactions between propofol and alfentanil both for the therapeutic and a major side effect, *i.e.*, change in hemodynamic function, to evaluate whether the combination of propofol and alfentanil is beneficial or detrimental to the patient in this regard during induction of anesthesia.

With the use of two computer-controlled infusion devices, we were able to study the interaction between propofol and alfentanil at blood and plasma concentrations that, after an appropriate period of time required for blood-effect site equilibration, may be expected to correspond closely with the concentrations in the biophase. With the two-compartment pharmacokinetic data of propofol<sup>12</sup> and the population pharmacokinetic data of alfentanil<sup>13</sup> entered into the computer controlled infusion device, fairly stable blood propofol and plasma alfentanil concentrations were obtained (figs. 1 and 2). The measured blood propofol concentrations closely corresponded to those predicted by the computer-controlled infusion device. The mea-

sured plasma alfentanil concentrations, however, exceeded those predicted by approximately 23%, which is in accordance with previous reports on the performance with this set of pharmacokinetic parameters.<sup>17</sup> The results of this study are comparable with those of previous studies on the pharmacodynamics of propofol. We found that in the absence of alfentanil, 50% of patients lost eyelash reflex and consciousness at blood propofol concentrations of 2.07 and 3.62  $\mu$ g/ml, respectively, compared to 2.07 and 3.40  $\mu$ g/ml, as reported recently.<sup>8</sup> Furthermore, Smith *et al.* similarly found that 50% of patients lost consciousness at a blood propofol concentration of 3.3  $\mu$ g/ml,<sup>20</sup> a concentration that decreased in the presence of fentanyl. The shape of the interaction curve between propofol and fentanyl described by Smith *et al.* remarkably resembles that found by us between propofol and alfentanil at equipotent opioid concentrations. In the presence of a plasma fentanyl concentration of 3 ng/ml, the propofol concentration associated with loss of consciousness in 50% of patients was reduced by 40%.<sup>20</sup> We found a similar decrease in the propofol concentration associated with loss of consciousness in 50% of patients in the presence of a plasma alfentanil concentration of

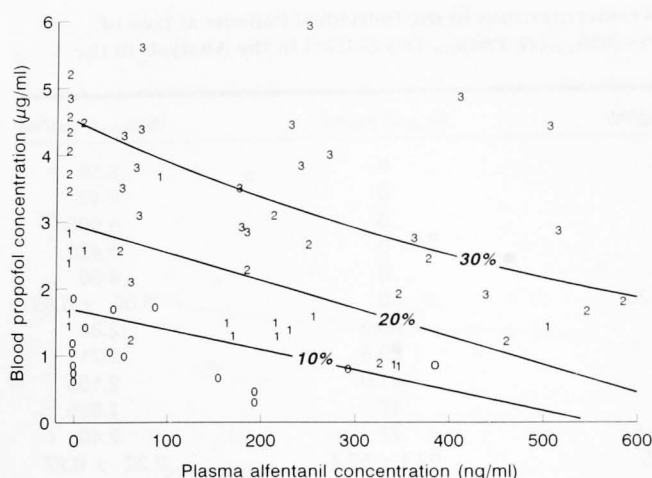


Fig. 5. The effect of the combination of propofol and alfentanil on systolic blood pressure. Numbers represent the percentile decrease in the systolic blood pressure at propofol and alfentanil concentration combinations at 12, 24, 36, 48, and 60 min after the start of the propofol infusion in the individual patients (0 = a decrease less than 10%; 1 = a decrease exceeding 10% but less than 20%; 2 = a decrease exceeding 20% but less than 30%; 3 = a decrease exceeding 30%). The curves represent propofol and alfentanil concentration combinations associated with the indicated decrease in the systolic blood pressure. The curves were obtained by logistic regression of the hemodynamic data versus the corresponding measured blood propofol concentrations and the (natural logarithm of the) plasma alfentanil concentrations. The 10% curve is described by the equation:  $\text{Prop}_{\text{SBP}10} = (0.0107 \cdot C_{\text{Alf}} - 5.9694) / -3.5443$ ,  $R^2 = 0.38$ . The 20% curve is described by the equation:  $\text{Prop}_{\text{SBP}20} = (0.0097 \cdot C_{\text{Alf}} - 6.8470) / -2.3212$ ,  $R^2 = 0.45$ . The 30% curve is described by the equation:  $\text{Prop}_{\text{SBP}30} = e^{((\text{CalF} \cdot 0.0061 - 6.1973) / -4.1134)}$ ,  $R^2 = 0.32$ .

approximately 122 ng/ml. Although the intravenous bolus dose potency ratio of fentanyl to alfentanil is approximately 5:1, the steady-state serum concentration potency ratio for changes in  $\text{EC}_{50}$  values of parameters derived from electroencephalogram analysis, has been reported to be 61:1.<sup>21</sup> Regarding the potentiation of the hypnotic effects of propofol by fentanyl and alfentanil, the potency ratio is in the same order of magnitude;  $122:3 = 41:1$ . This suggests, not surprisingly, that the interaction between propofol and fentanyl probably is propagated through a similar mechanism as that between propofol and alfentanil.

Both the interaction curves for loss of eyelash reflex and for loss of consciousness were best fitted by an isobole with the concavity upward, indicating a supraadditive interaction with respect to these clinical endpoints. In general, the slope of the concavity of the interaction curve is representative for the magnitude of the described interaction, and is mathematically de-

scribed by the parameter  $\epsilon$  in the mechanistic interaction model (Appendix). The interaction between propofol and alfentanil for loss of eyelash reflex and for loss of consciousness is rather weak ( $\epsilon = 3.1$ , and 3.0 respectively), compared to the interaction for the suppression of responses to intraoperative stimuli during lower abdominal surgery ( $\epsilon = 26.5$ ).<sup>9</sup> Similarly, the degree of interaction between propofol and fentanyl was much stronger for the suppression of responses to skin incision than that for loss of consciousness.<sup>20</sup> Apparently, for the combination of propofol with fentanyl or alfentanil, the strength of the stimulus affects the magnitude of the interaction, i.e., the stronger the stimulus (testing of responsiveness to intraoperative surgical stimuli > testing of responsiveness to skin incision > testing of eyelash reflex or consciousness), the stronger the interaction between propofol and the opioid. Similarly, Kissin *et al.* previously reported on the changing character of the interaction between bar-

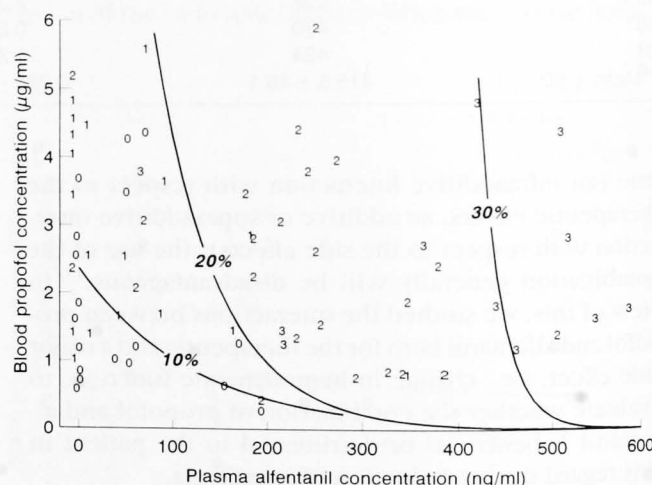


Fig. 6. The effect of the combination of propofol and alfentanil on heart rate. The numbers represent the percentile decrease in heart rate at propofol and alfentanil concentration combinations at 12, 24, 36, 48, and 60 min after the start of the propofol infusion in the individual patients (0 = a decrease less than 10%; 1 = a decrease exceeding 10% but less than 20%; 2 = a decrease exceeding 20% but less than 30%; 3 = a decrease exceeding 30%). The curves represent propofol and alfentanil concentration combinations associated with the indicated decrease in the heart rate. The curves were obtained by logistic regression of the hemodynamic data versus the corresponding measured blood propofol concentrations and the (natural logarithm of the) plasma alfentanil concentrations. The 10% curve is described by the equation:  $\text{Prop}_{\text{HR}10} = e^{((\text{CalF} \cdot 0.0096 - 0.9913) / -1.1405)}$ ,  $R^2 = 0.22$ . The 20% curve is described by the equation:  $\text{Prop}_{\text{HR}20} = e^{((\text{CalF} \cdot 0.0142 - 2.8145) / -0.9544)}$ ,  $R^2 = 0.37$ . The 30% curve is described by the equation:  $\text{Prop}_{\text{HR}30} = e^{((\text{CalF} \cdot 0.0086 - 3.9529) / -0.2077)}$ ,  $R^2 = 0.21$ .

Table 3. Fitted Values of the Possibilities of an Additive Decrease in Systolic Blood Pressure

10% decrease in SBP*
10% decrease in SBP†
20% decrease in SBP*
20% decrease in SBP†
30% decrease in SBP*
30% decrease in SBP†
10% decrease in HR*
10% decrease in HR†
20% decrease in HR*
20% decrease in HR†
30% decrease in HR*
30% decrease in HR†

SBP = systolic blood pressure; HR = heart rate.

\*  $\beta_0$ ,  $\beta_1$ ,  $\beta_2$ , and  $R^2$ , of the function

†  $\beta_0$ ,  $\beta_1$ ,  $\beta_2$ , and  $R^2$ , of the function

biturates and morphine to the propofol-opioid morphine interaction strength of stimulation.<sup>22</sup> agents in rats turned from reflex (an endpoint generated with hypnosis in humans) blockade of motor response point generally accepted in humans).<sup>4,23</sup>

Why does the magnitude of two anesthetic agents vary in general, biologic phenomena weaker the intensity of the concentration of the response and no-response to the range of concentrations is effective. As a intensity of the stimulus becomes to distinguish between a straight line, regardless of the concentration of the former. Because of this, to substantiate the true between two agents at weak at more profound stimulations between drugs increasing stimulus intensity of interaction between the changed. This argument

## PHARMACODYNAMIC INTERACTION OF PROPOFOL AND ALFENTANIL

**Table 3. Fitted Values of the Coefficients  $\pm$  SE of the Two Logistic Regressions That Were Performed to Explore the Possibilities of an Additive and of a Nonadditive Interaction between Propofol and Alfentanil for the 10%, 20%, and 30% Decrease in Systolic Blood Pressure, the 10%, 20%, and 30% Decrease in Heart Rate, and Their Correlation Coefficients**

	$\beta_0 \pm \text{SE}$	$\beta_1 \pm \text{SE}$	$\beta_2 \pm \text{SE}$	$R^2$
10% decrease in SBP*	5.9694 $\pm$ 1.9918	-3.5443 $\pm$ 1.1436	-0.0107 $\pm$ 0.0040	0.38
10% decrease in SBP†	2.5136 $\pm$ 1.0866	-5.2159 $\pm$ 1.6123	-0.0126 $\pm$ 0.0042	0.38
20% decrease in SBP*	6.8470 $\pm$ 1.5653	-2.3212 $\pm$ 0.5280	-0.0097 $\pm$ 0.0029	0.45
20% decrease in SBP†	5.0446 $\pm$ 1.2459	-4.8064 $\pm$ 1.0764	-0.0097 $\pm$ 0.0031	0.44
30% decrease in SBP*	5.8035 $\pm$ 1.4181	-1.3080 $\pm$ 0.3469	-0.0055 $\pm$ 0.0022	0.29
30% decrease in SBP†	6.1973 $\pm$ 1.6619	-4.1134 $\pm$ 1.1648	-0.0061 $\pm$ 0.0024	0.32
10% decrease in HR*	1.4360 $\pm$ 0.7519	-0.5252 $\pm$ 0.2410	-0.0092 $\pm$ 0.0029	0.21
10% decrease in HR†	0.9913 $\pm$ 0.5705	-1.1405 $\pm$ 0.4820	-0.0096 $\pm$ 0.0030	0.22
20% decrease in HR*	3.1862 $\pm$ 0.9695	-0.4280 $\pm$ 0.2485	-0.0140 $\pm$ 0.0033	0.36
20% decrease in HR†	2.8145 $\pm$ 0.7599	-0.9544 $\pm$ 0.5234	-0.0142 $\pm$ 0.0032	0.37
30% decrease in HR*	3.8992 $\pm$ 1.1121	-0.0390 $\pm$ 0.2698	-0.0086 $\pm$ 0.0024	0.20
30% decrease in HR†	3.9529 $\pm$ 0.9731	-0.2077 $\pm$ 0.6139	-0.0086 $\pm$ 0.0023	0.21

SBP = systolic blood pressure; HR = heart rate.

\*  $\beta_0$ ,  $\beta_1$ ,  $\beta_2$ , and  $R^2$ , of the function:  $\text{Prop}_{\text{Effect}} = (-\beta_2 \cdot C_{\text{Alf}} - \beta_0)/\beta_1$ , exploring the possibility of an additive interaction.

†  $\beta_0$ ,  $\beta_1$ ,  $\beta_2$ , and  $R^2$ , of the function:  $\text{Prop}_{\text{Effect}} = e^{\frac{[(C_{\text{Alf}} - \beta_2) - \beta_0]}{\beta_1}}$ , exploring the possibility of a nonadditive interaction.

biturates and morphine in rats. However, in contrast to the propofol-opioid interaction, the barbiturate-morphine interaction weakened with increasing strength of stimulation.<sup>22</sup> The interaction between these agents in rats turned from synergistic for loss of righting reflex (an endpoint generally accepted to correspond with hypnosis in humans), to antagonistic for the blockade of motor responses, to tail clamping (an endpoint generally accepted to correspond with anesthesia in humans).<sup>4,23</sup>

Why does the magnitude of the interaction between two anesthetic agents vary for different endpoints? In general, biologic phenomena are nonlinear.<sup>15</sup> The weaker the intensity of the stimulus studied, the lower the concentrations of the agents at which both response and no-response data can be gathered relative to the range of concentrations at which the combinations is effective. As a consequence, the weaker the intensity of the stimulus studied, the more difficult it becomes to distinguish between the interaction curve and a straight line, regardless of the true shape of the former. Because of this, it is generally more difficult to substantiate the true nature of the interaction between two agents at weaker stimuli compared to that at more profound stimuli. Hence, synergistic interactions between drugs tend to additivism with decreasing stimulus intensity, although the mechanism of interaction between these agents might remain unchanged. This argument supports the hypothesis that

for all studied endpoints propofol and alfentanil generate their actions in one and the same way. Conversely, several studies support the hypothesis that the mechanism of (inter)action by which the various effects of a combination of intravenous anesthetics is accomplished is effected through different pathways at different sites in the central nervous system.<sup>24,25</sup> Loss of consciousness induced by the combination of propofol and alfentanil might be the result of the binding to a different receptor site than that producing unresponsiveness to surgical stimuli. The origins of the differential analgesic and sedative effects of opioids have long been of interest to pharmacologists. Whereas the analgesic effects of opioids are generated through receptor binding in, among others, the periaqueductal gray matter of the brain stem and in the spinal cord; morphine, and other  $\mu$ - and  $\delta$ -opioid receptor agonists were found to selectively induce hypnotic effects when injected locally into the nucleus of the solitary tract in cats.<sup>24</sup> In contrast, morphine promoted wakefulness after administration at the medial pontine reticular formation.<sup>25</sup> These data suggest that the various actions of opioids are dependent on locus, and the interactions between opioids and other intravenous agents might thus be effected at different sites, and thereby be different in magnitude or character.

In addition to the therapeutic effects of the combination of propofol and alfentanil, we studied the in-



## PHARMACODYNAMIC INTERACTION OF PROPOFOL AND ALFENTANIL

mododynamic depression. One should keep in mind, however, that the interactions described in this study were determined in patients in the absence of noxious stimuli. The implications of these data might be different in patients in whom induction of anesthesia is rapidly followed by intubation and/or surgical stimuli.

In conclusion, this study demonstrates the marked decrease in blood propofol concentrations required for loss of eyelash reflex and loss of consciousness, in the presence of alfentanil. Propofol and alfentanil interact in a supraadditive way for loss of eyelash reflex and loss of consciousness. Furthermore, alfentanil enhances the depressant effects of propofol on the systolic blood pressure and heart rate. As a result, within the concentration ranges studied, and in the absence of noxious stimuli, the supplementation of propofol by alfentanil does not increase the hemodynamic stability during induction of anesthesia in ASA physical status I patients.

## Appendix

*Data Analysis of the Interaction for Loss of Eyelash Reflex and Loss of Consciousness*

The mid-range propofol concentrations data calculated from the raw data for loss of eyelash reflex and loss of consciousness in the individual patients were related to the corresponding mid-range plasma alfentanil concentrations with a mechanistic model over all patients ( $n = 19$ ) by an unweighted least-squares nonlinear regression analysis. The mechanistic function is described by the equation:

$$\frac{Prop_{Effect}(i)}{EC_{50Prop}} + \frac{Alf_{Effect}(i)}{EC_{50Alf}} + \epsilon \cdot \frac{Prop_{Effect}(i)}{EC_{50Prop}} \cdot \frac{Alf_{Effect}(i)}{EC_{50Alf}} = I, \quad (A1)$$

where  $Prop_{Effect}(i)$  and  $Alf_{Effect}(i)$  are the mid-range blood propofol and mid-range plasma alfentanil concentration determined in the  $i^{th}$  individual, the Effect is loss of eyelash reflex (LOER) or loss of consciousness (LOC), and  $EC_{50Prop}$  and  $EC_{50Alf}$  are the blood propofol and plasma alfentanil concentrations at which 50% of patients lose the eyelash reflex or consciousness when these agents are given as sole agents, and  $\epsilon$  is a dimensionless parameter characterizing the shape of the curve (with  $\epsilon = 0$ : the result is a straight line suggesting additivity, with  $\epsilon = 0$  the result is a curved line suggesting nonadditivity). Both the possibilities of an additive, and a nonadditive interaction were explored. The possibility of an additive interaction between alfentanil and propofol was examined by the equation (derived from equation A1, assuming  $\epsilon = 0$ ):

$$Prop_{Effect}(i) = EC_{50Prop} - \frac{Alf_{Effect}(i) \cdot EC_{50Prop}}{EC_{50Alf}} \quad (A2)$$

The possibility of a nonadditive interaction between alfentanil and propofol was examined by the equation (derived from equation A1):

$$Prop_{Effect}(i) = \frac{EC_{50Prop} \cdot (EC_{50Alf} - Alf_{Effect}(i))}{EC_{50Alf} + \epsilon \cdot Alf_{Effect}(i)} \quad (A3)$$

The residual sum of squares of both fitted curves for loss of eyelash reflex and loss of consciousness were compared with an F-test to determine which fitted curve correlated best with the data used in the analysis (table A1). For loss of eyelash reflex (fig. 3), a significant difference was found between the residual sums of squares of the models exploring an additive and a nonadditive interaction between propofol and alfentanil (residual SS: 3015174 vs. SS: 2017698,  $F = 7.9$ ,  $P < 0.05$ ). For loss of consciousness (fig. 4), the residual sum of squares of the model exploring a nonadditive interaction between propofol and alfentanil was also significantly smaller compared to that of the model exploring a possible additive interaction (residual SS: 6304605 vs. SS: 4648040,  $F = 5.7$ ,  $P < 0.05$ ). The interaction between propofol and alfentanil is thus best characterized by a non-additive function both for loss of eyelash reflex and for loss of consciousness. According to the isobolographic method,<sup>15</sup> the interaction between propofol and alfentanil was therefore judged to be synergistic both for loss of eyelash reflex and for loss of consciousness. Both for loss of eyelash reflex and for loss of consciousness, the negative values for  $EC_{50Alf}$  and  $\epsilon$  indicate that the curve corresponding with this function does not cross the y-axis, but runs asymptotically to lines corresponding with propofol concentrations of 0.67  $\mu\text{g/ml}$  and 1.21  $\mu\text{g/ml}$ , respectively. This suggests that alfentanil is not capable of the induction of loss of eyelash reflex and loss of consciousness in the absence of propofol, which is in correspondence with previous reports on the pharmacodynamics of alfentanil.<sup>9,29-31</sup>

*Data Analysis of the Interaction with Respect to Changes in Hemodynamic Parameters*

The effect of propofol and alfentanil on hemodynamic function was characterized by defining the propofol and alfentanil concentration combinations that caused a 10%, 20%, and 30% decrease in the arterial systolic blood pressure and heart rate by logistic regression. Immediate preinduction systolic blood pressure and heart rate values were used as control data. The percentile decrease in the systolic blood pressure and heart rate values at 12, 24, 36, 48, and 60 min, i.e., the times just before an increase in the target propofol concentration, were used in the analysis versus the corresponding measured blood propofol and plasma alfentanil concentrations. For both hemodynamic parameters, three logistic regressions were performed to obtain hemodynamic lines representing blood propofol and plasma alfentanil concentrations associated with a 10%, 20%, and 30% decrease in the systolic blood pressure and heart rate. In the logistic regression analysis, no-response was defined as a percentile decrease in the systolic blood pressure or heart rate of less than 10%, 20%, or 30%, whereas a response was defined as a percentile decrease in systolic blood pressure or heart rate exceeding 10%, 20%, or 30%. For both hemodynamic parameters, the logistic regression was performed twice for each curve to explore both the possibilities of an additive interaction (a regression of the presence or absence of a response to one of the stimuli vs. the measured blood propofol and the plasma alfentanil concentrations), as well as of a nonadditive interaction (a regression of the presence or absence of a response vs. the measured plasma alfentanil and the natural logarithm of the measured blood propofol concentrations.<sup>29</sup> The logistic function is described by the equation:

$$\pi = \frac{e^{\beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2}}{1 + e^{\beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2}} \quad (A4)$$

**Table A1. Values of the Estimates of the Concentrations of Propofol and Alfentanil Associated with a 50% Probability of No Response ( $EC_{50_{Prop}}$ ,  $EC_{50_{Alf}}$ ),  $\epsilon$ , the Residual Sum of Squares (RSS), and the Correlation Coefficients ( $R^2$ ) for the Two Possible Interactions (Additivity or Nonadditivity) for Loss of Eyelash Reflex and Loss of Consciousness**

Stimulus	$EC_{50_{Prop}}$ ( $\mu$ g/ml)	$EC_{50_{Alf}}$ (ng/ml)	$\epsilon$	RSS	$R^2$
Loss of eyelash reflex*	1.78	691.2	0	3015174	0.53
Loss of eyelash reflex†	2.07	-198.6	-3.08	2017698‡	0.68
Loss of consciousness*	3.20	731.7	0	6304605	0.63
Loss of consciousness†	3.62	-240.4	-2.98	4648040‡	0.72

\* Exploring the possibility of an additive interaction.

† Exploring the possibility of a nonadditive interaction.

‡ Significantly different from the residual sum of squares corresponding with the model describing the possibility of an additive interaction. The interaction between propofol and alfentanil for loss of eyelash reflex and loss of consciousness was therefore decided to be synergistic. The negative values for  $EC_{50_{Alf}}$  and  $\epsilon$  in these functions indicate that the curves corresponding with these functions do not cross the x-axis, but run asymptotically to a line corresponding with a propofol concentration of 0.67  $\mu$ g/ml for loss of eyelash reflex and 1.21  $\mu$ g/ml for loss of consciousness. This suggests that according to this function alfentanil is not capable of the induction of loss of eyelash reflex and loss of consciousness in the absence of propofol.

where  $\pi$  is the probability of no response,  $x_1$  is the blood propofol or the natural logarithm of the blood propofol concentration,  $x_2$  is the plasma alfentanil concentration, and  $\beta_0$ ,  $\beta_1$ , and  $\beta_2$  are the coefficients describing the shape of the curve. The possibility of an additive interaction between propofol and alfentanil was examined by the equation (derived from equation A4):

$$\text{Prop}_{\text{Effect}} = \frac{(-\beta_2 \cdot C_{Alf} - \beta_0)}{\beta_1} \quad (\text{A5})$$

The possibility of a nonadditive interaction between propofol and alfentanil was examined by the equation (derived from equation A4):

$$\text{Prop}_{\text{Effect}} = e^{((C_{Alf} - \beta_2) - \beta_0) / \beta_1}, \quad (\text{A6})$$

where  $\text{Prop}_{\text{Effect}}$  is the blood propofol concentration associated with any of the studied changes in both hemodynamic parameters in 50% of patients, Effect is the 10%, 20%, or 30% decrease in systolic blood pressure (SBP10, SBP20, or SBP30), or heart rate (HR10, HR20, HR30),  $C_{Alf}$  is the corresponding plasma alfentanil concentration, and  $\beta_0$ ,  $\beta_1$ , and  $\beta_2$  are the coefficients describing the shape of the curves. For each curve of both hemodynamic parameters the nature of the interaction (additive or nonadditive) was then determined on the basis of the magnitude of the correlation between the original data and both fitted curves. The fitted curve with the highest correlation with the original data was judged to be the optimal fitted line, and to represent the true nature of the interaction between propofol and alfentanil for that stimulus. Figures 5 and 6 show for each hemodynamic parameter the optimal curves and the raw data. Table 3 displays for each stimulus the  $\beta_0$ ,  $\beta_1$ ,  $\beta_2$ , and the  $R^2$ , of both models that were explored.

## References

1. Katzung BG: Basic and Clinical Pharmacology, Los Altos, Lange Medical Publications, 1984, pp 810-6
2. Schwiager IM, Hall RI, Szlam F, Hug CC Jr: Anesthetic interactions of midazolam and fentanyl: Is there acute tolerance to the opioid? *ANESTHESIOLOGY* 1989; 70:667-71

3. Vinik HR, Bradley EL, Kissin I: Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg* 1989; 69:213-7
4. Kissin I, Mason JO, Bradley EL Jr: Morphine and fentanyl hypnotic interaction with thiopental. *ANESTHESIOLOGY* 1987; 67:331-5
5. Short TG, Chui PT: Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; 67:539-45
6. Short TG, Plummer JL, Chui PT: Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. *Br J Anaesth* 1992; 69:162-7
7. Ben-Shlomo I, Abd-El-Khalim H, Ezry J, Zohar S, Tverskoy M: Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth* 1990; 64:45-7
8. Vuyk J, Engbers FHM, Lemmens HJM, Burm AGL, Vletter AA, Gladines MPRR, Bovill JG: Pharmacodynamics of propofol in female patients. *ANESTHESIOLOGY* 1992; 77:3-9
9. Vuyk J, Lim T, Engbers FHM, Burm AGL, Vletter AA, Bovill JG: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in female patients. *ANESTHESIOLOGY* 1995; 83:8-22
10. Jacobs JR, Reves JG: Effect site equilibration time is a determinant of induction dose requirements. *Anesth Analg* 1993; 76:1-6
11. Lemmens HJM, Bovill JG, Hennis PJ, Gladines MPRR, AGL Burm: Alcohol consumption alters the pharmacodynamics of alfentanil. *ANESTHESIOLOGY* 1989; 71:669-74
12. Shafer A, Doze VA, Shafer SL, White PF: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. *ANESTHESIOLOGY* 1988; 69:348-56
13. Maitre PO, Vozeh S, Heykants J, Thomson DA, Stanski DR: Population pharmacokinetics of alfentanil: The average dose-plasma concentration relationship and interindividual variability in patients. *ANESTHESIOLOGY* 1987; 66:3-12
14. Lemmens HJM, Burm AGL, Bovill JG, Hennis PJ, Gladines MPRR: Pharmacodynamics of alfentanil. The role of plasma protein binding. *ANESTHESIOLOGY* 1992; 76:65-70
15. Berenbaum MC: What is synergy? *Pharmacol Rev* 1989; 41:93-141
16. Schwinghammer TL, Kroboth PD: Basic concepts in pharmacodynamic modeling. *J Clin Pharmacol* 1988; 28:388-94

## PHARMACODYNAMIC INTERACTION OF PROPOFOL AND ALFENTANIL

17. Raemer DB, Buschman A, Varvel JR, Philip BK, Johnson MD, Stein DA, Shafer SL: The prospective use of population pharmacokinetics in a computer-driven infusion system for alfentanil. *ANESTHESIOLOGY* 1990; 73:66-72
18. Glass PSA, Jacobs JR, Smith LR, Ginsberg B, Quill TJ, Bai SA, Reves JG: Pharmacokinetic model-driven infusion of fentanyl: Assessment of accuracy. *ANESTHESIOLOGY* 1990; 73:1082-90
19. Shafer SL, Varvel JR, Aziz N, Scott JC: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. *ANESTHESIOLOGY* 1990; 73:1091-1102
20. Smith C, McEwan E, Jhaveri R, Wilkinson M, Goodman D, Smith R, Canada AT, Glass P: The interaction of fentanyl on the CP<sub>50</sub> of propofol for loss of consciousness and skin incision. *ANESTHESIOLOGY* 1994; 81:820-8
21. Scott C, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; 240:159-66
22. Kissin I, Stanski DR, Brown PT, Bradley EL: Pentobarbital-morphine anesthetic interactions in terms of intensity of noxious stimulation required for arousal. *ANESTHESIOLOGY* 1993; 78:744-9
23. Kissin I, Mason JO, Bradley EL Jr: Morphine and fentanyl interaction with thiopental in relation to movement response to noxious stimulation. *Anesth Analg* 1986; 65:1149-54
24. Reinoso-Barbero F, de Andrés I: Effects of opioid microinjections in the nucleus of the solitary tract on the sleep-wakefulness cycle states in cats. *ANESTHESIOLOGY* 1995; 82:144-52
25. Keifer JC, Baghdoyan HA, Lydic R: Sleep disruption and increased apneas after pontine microinjection of morphine. *ANESTHESIOLOGY* 1992; 77:973-82
26. Boer F, Ros P, Bovill JG, Van Brummelen P, Van der Krogt J: Effect of propofol on peripheral vascular resistance during cardiopulmonary bypass. *Br J Anaesth* 1990; 65:184-9
27. Pagel PS, Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. *ANESTHESIOLOGY* 1993; 78:100-8
28. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J: Effect of propofol anesthesia on baroreflex activity in humans. *Anesth Analg* 1987; 66:1115-20
29. Sebel PS, Glass PSA, Fletcher JE, Murphy MR, Gallagher C, Quill T: Reduction of the MAC of desflurane with fentanyl. *ANESTHESIOLOGY* 1992; 76:52-9
30. Hall RI, Szlam F, Hug CC: The enflurane-sparing effect of alfentanil in dogs. *Anesth Analg* 1987; 66:1287-91
31. Hug CC: Does opioid anesthesia exist? *ANESTHESIOLOGY* 1990; 73:1-4