■ CLINICAL INVESTIGATIONS

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The Pharmacodynamic Interaction of Propofol and Alfentanil during Lower Abdominal Surgery in Women

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Background: **Propofol and alfentanil are frequently combined to provide general anesthesia. The purpose of this study was to characterize the pharmacodynamic interaction between propofol and alfentanil for several clinically relevant end points.**

Methods: **Twenty-one women, aged 20–55 yr, scheduled for lower abdominal surgery, were randomly assigned in a double-blind manner to one of three groups to receive a computer-controlled infusion of propofol with target concentrations of 2, 4, or 6 μg/ml. In addition, all patients received computer-controlled infusion of alfentanil (initial target concentration 50 ng/ml). While the target concentration of propofol was maintained constant, the target concentration of alfentanil was varied in steps of 10–50 ng/ml according to the presence or absence of patient responses to perioperative stimuli. Arterial blood samples for alfentanil and propofol determination were taken at clinically relevant stimuli. Alfentanil–propofol interactions for laryngoscopy, intubation, skin incision, the opening of the peritoneum, and awakening were determined by logistic regression over the three groups (n = 21). The alfentanil concentrations associated with a 50% probability (EC_{50}s) of suppression of responses to intraabdominal surgical stimuli, as determined by logistic regression in the individual patients, were related to corresponding mean blood propofol concentrations by nonlinear regression analysis.**

Results: **With blood propofol concentrations increasing from 2 to 10 μg/ml, the EC_{50} of alfentanil decreased from 170 to 25 ng/ml for laryngoscopy, from 280 to 23 ng/ml for intubation, from 259 to 9 ng/ml for the opening of the peritoneum, and from 209 to 16 ng/ml for the intraabdominal surgical stimuli. With plasma alfentanil concentrations increasing from 10 to 150 ng/ml, the EC_{50} of propofol for the regaining of consciousness decreased from 3.8 to 0.8 μg/ml.**

Discussion: **We defined the pharmacodynamic interaction between propofol and alfentanil for suppression of responses to perioperative stimuli during lower abdominal surgery. We conclude that propofol reduces alfentanil requirements for all studied clinical end points. In addition, alfentanil decreases propofol concentrations at which patients regain consciousness. (Key words: Analgesics, opioids: alfentanil. Anesthetics, intravenous: alfentanil; propofol. Anesthetic techniques: computer-controlled infusion. Interactions (drug): alfentanil–propofol. Pharmacodynamics: alfentanil; propofol.**

This article is accompanied by an editorial. Please see: Stanski DR, Shafer SL: Quantifying anesthetic drug interaction: Implications for drug dosing. ANESTHESIOLOGY 83:1–5, 1995.

FREQUENTLY in clinical practice, inhalational or intravenous anesthetic agents are combined to reduce the dose requirements of the individual agents, to diminish the incidence of side effects during induction and maintenance of anesthesia, or to increase the speed of recovery. Because anesthetic agents are combined so often, numerous studies have been performed to evaluate the effects of various combinations. Most combinations of inhalational agents have been shown to exert additive anesthetic effects.[1] For intravenous anesthetics, however, the effect of various combinations is less predictable, probably because of the wider variability in mechanisms of action of intravenous agents of different classes (*e.g.,* barbiturates and opioids). Combinations of intravenous agents have been found to exert additive,[2] synergistic,[3–7] or less than additive[8] effects. To date, studies on the interaction of intravenous agents in humans have focused mainly on effects with respect to the induction of anesthesia.

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Materials and Methods

With approval of the local medic
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Determination of the intraoperative concentration–response relations of combinations of sedative and analgesic agents that are commonly used in total intravenous anesthesia would provide the data essential for optimal application of this technique.

The induction characteristics of propofol when given as the sole agent[9] and when combined with fentanyl# have been described. The concentration associated with a 50% probability (EC_{50}) of loss of consciousness is 3.4 μg/ml and is not affected by the concomitant administration of fentanyl.# Recently we described the concentration–response relations of alfentanil for various clinically relevant perioperative end points at a single fixed blood propofol concentration.[10] It is likely that the plasma alfentanil concentration–response relations vary with the blood propofol concentration.

We therefore examined the influence of the blood propofol concentration on the alfentanil concentration–response relations for several clinical relevant stimuli in women undergoing lower abdominal surgery. In addition, we studied the recovery characteristics after anesthesia with three propofol–alfentanil concentration regimens.

Materials and Methods

With approval of the local Medical Ethics Committee and after obtaining informed consent, 21 women (American Society of Anesthesiologists physical status 1, aged 20–55 yr) scheduled for lower abdominal surgery were studied. 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 alcohol/day or smoking more than 10 cigarettes/day were also excluded from the study.[11] The patients were randomly assigned to one of three study groups to receive, in a double-blind manner, a controlled infusion of propofol with target concentrations of 2 μg/ml (group A), 4 μg/ml (group B), or 6 μg/ml (group C), in combination with alfentanil.

The solutions of propofol were prepared by an anesthesiologist who took no further part in the study. For patients in group A, 40 ml glucose 5% was added to 20 ml propofol (10 mg/ml) to obtain 60 ml propofol, 3.33 mg/ml. For patients in group B, 20 ml glucose 5% was added to 40 ml propofol (10 mg/ml) to obtain 60 ml propofol, 6.66 mg/ml. For patients in group C, the propofol solution was not diluted. The investigator was blinded to the propofol solutions being used.

A pocket computer (Portfolio, Atari, Okasagi, Japan) provided with three-compartment population pharmacokinetic data[12] for alfentanil, which were adjusted for patient gender, weight, and age, was used to control an infusion pump (Ohmeda 9000, Madison, WI) for the infusion of alfentanil. A second Atari Portfolio computer, provided with three-compartment pharmacokinetic data[13] for propofol, was used to control another Ohmeda 9000 infusion pump for the infusion of propofol.

One hour preoperatively all patients received temazepam, 10–20 mg orally. In the operating room electrocardiographic electrodes were attached, and two electrodes were fixed on the ulnar side of a wrist for determination of muscle relaxation with a neuromuscular monitoring device (Myotest DBS, IBC Danica, Denmark). An intravenous cannula was inserted into a large forearm vein for infusion of alfentanil and propofol, and a cannula was inserted into a radial artery for continuous measurement of arterial blood pressure and collection of blood samples.

After the subjects breathed 100% oxygen for 3 min, 0.02 mg/kg pancuronium was given intravenously, and then anesthesia was induced by computer-controlled infusion of propofol with a target concentration of 6 μg/ml, to be achieved in 2 min. Because the propofol concentrations in the syringes in the patients of the three groups differed, the real target concentrations were 2, 4, and 6 μg/ml in the patients of groups A, B, and C, respectively. This infusion was maintained throughout the surgical procedure until the peritoneum was closed.

Eight minutes after the start of the propofol infusion, the alfentanil infusion was initiated with a target concentration of 50 ng/ml, to be achieved in 1 min. Fourteen minutes (*i.e.*, four times the T½ke0 of propofol**) after the start of the propofol infusion, provided that the patients had lost consciousness, 1 mg/kg succinylcholine was given intravenously; laryngoscopy was performed; and the trachea of the patient was intubated. If a patient had not lost consciousness by 14 min after the start of the propofol infusion, the target alfentanil concentration was increased by 100–200 ng/ml to induce unconsciousness.

Smith S, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Canada A, Glass PSA: Reduction of propofol Cp_{50} by fentanyl (abstract). ANESTHESIOLOGY 77:A340, 1992.

** Schüttler J, Schwilden H, Stoeckel H: Pharmacokinetic-dynamic modeling of Diprivan (abstract). ANESTHESIOLOGY 65:A549, 1986.

To determine optimally the concentration–effect relation of alfentanil for laryngoscopy, a second and third laryngoscopy were performed at different target alfentanil concentrations and the presence or absence of a response noted. When patients did not respond to the first or second laryngoscopy, the target alfentanil concentration was decreased by 25–50 ng/ml. When patients did respond to the first or second laryngoscopy, the target alfentanil concentration was increased by 25–50 ng/ml for the next laryngoscopy. Four minutes after a new target alfentanil concentration had been reached, the next laryngoscopy was carried out. For each patient, information on response and no-response to laryngoscopy was thus obtained. A response to laryngoscopy was defined by the same criteria as those used to define inadequate anesthesia (see below). After intubation, the lungs of the patients were ventilated with 30% oxygen in air to an end-tidal carbon dioxide partial pressure of 34–38 mmHg.

The target propofol concentration was maintained constant until the peritoneum was closed. Then the target propofol concentration was reduced by 50% and finally discontinued approximately 10 min before skin closure. The alfentanil administration was continued and changed in response to the presence or absence of signs of inadequate anesthesia. When signs of inadequate anesthesia developed, the target alfentanil concentration was increased by 10–50 ng/ml for 8 min. When no signs of inadequate anesthesia were observed for 8 min, the alfentanil target concentration was decreased by 10–50 ng/ml. The alfentanil infusion was discontinued approximately 10 min before skin closure.

Inadequate anesthesia was defined by the following criteria[14]:

1. an increase in systolic blood pressure by more than 15 mmHg above normal for that patient, with normal systolic blood pressure defined as the mean of three systolic blood pressure measurements from admission until premedication
2. a heart rate exceeding 90 beats/min in the absence of hypovolemia
3. other autonomic signs such as sweating or flushing
4. somatic responses such as movements or swallowing

During the study each patient was observed continuously for evidence of inadequate anesthesia as defined above by three persons: a resident in anesthesia, an anesthesiologist, and a medical student. If inadequate anesthesia was detected it was accepted only if verified by all three observers. Neuromuscular transmission was monitored by percutaneous stimulation of the ulnar nerve by using the train-of-four method. To facilitate identification of somatic responses, pancuronium was given at a minimal dose as necessary for surgery.

After skin closure, neuromuscular blockade was antagonized by 1 mg intravenous neostigmine and 0.5 mg intravenous atropine. Once spontaneous ventilation had been established, if the end-tidal carbon dioxide partial pressure was less than 46 mmHg, tidal volume more than 7 ml/kg, and respiratory rate more than 10 breaths/min, the trachea was extubated. If 10 min after skin closure patients did not breathe adequately, respiratory depression was antagonized by 40 μg intravenous naloxone, repeated every 2 min, if required.

After skin closure, the patients were tested every 2 min by verbal commands to evaluate return of consciousness. Return of consciousness was defined as the positive response to a verbal command. After the trachea had been extubated, the patient was transported to the recovery room. Twenty-four hours postoperatively, the patients were interviewed to evaluate possible side effects and any recall of intraoperative events.

To evaluate the speed of recovery, the patients were asked to perform a "deletion-of-*p*'s" test.[15,16] The patients were asked to delete in 2 min as many *p*'s as possible on a sheet of closely packed, randomly typed letters. Only correctly deleted *p*'s were counted. The test was done preoperatively and 5, 30, 60, 120, and 240 min postoperatively.

Blood Samples and Assays

Arterial blood samples, for measurement of the plasma alfentanil concentration, were collected in heparinized syringes at laryngoscopy, intubation, skin incision, the opening of the peritoneum, and awakening. Samples were also obtained 4 and 8 min after a predicted alfentanil target concentration was achieved during the intraoperative period. Every 20–30 min an additional arterial blood sample for the determination of blood propofol concentrations was collected in glass tubes containing potassium oxalate. The concentrations of alfentanil in plasma were determined by capillary gas chromatography.[17] The detection limit was approximately 0.2 ng alfentanil per ml plasma. The coefficient of variation of the gas chromatographic method did not exceed 5% in the concentration range encountered in this study. The blood propofol concentrations were measured by reversed-phase high-performance liquid chromatography.[9] The detection limit was ap-

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Data Analysis

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proximately 5 ng propofol/ml blood. The coefficient of variation for this chromatography method did not exceed 7% in the concentration range encountered in this study.

Data Analysis

Patient characteristics, duration of anesthesia, percentage of anesthesia time during which all four twitches of the train-of-four were present, and total dose of alfentanil were compared among groups using one-way analysis of variance followed by the Student-Newman-Keul test if appropriate.

For each patient only one data point was available for intubation, skin incision, the opening of the peritoneum, and awakening, whereas only two data points were used for the analysis of the interaction at laryngoscopy (the highest plasma alfentanil concentration at which a response was noted, and the lowest plasma alfentanil at which no response was noted). The interaction between propofol and alfentanil for suppression of the responses to these stimuli was therefore determined over all patients (n = 21), for each stimulus separately, by logistic regression[18] (see appendix) using the statistical software program NCSS (Number Cruncher Statistical System, Kaysville, UT). For each stimulus both the possibilities of an additive, and nonadditive interaction were explored. On the basis of the isobolographic method,[19] the nature of the interaction (additive or nonadditive) between propofol and alfentanil was determined, for each stimulus separately, by examining the correlation between the original data and the two fitted curves.

In contrast, for the intraabdominal part of surgery, multiple data were available per patient. The concentration–effect relation of alfentanil for suppression of responses to the intraabdominal part of surgery was therefore determined for each patient separately by logistic regression (see appendix) using the statistical software program NCSS. In addition, the mean propofol concentration was calculated for each patient by averaging the concentrations measured in all blood samples collected from that patient intraoperatively. The EC_{50} of alfentanil for suppression of responses to the intraabdominal part of surgery in the individual patients was then related to the corresponding mean blood propofol concentrations by an unweighted least-squares nonlinear regression analysis over all patients (n = 21) (see appendix). Both the possibilities of an additive, and nonadditive interaction were explored. According to the isobolographic method[19] the nature of interaction between propofol and alfentanil for suppression of responses intraoperatively was then determined, comparing the residual sum of squares of both fitted curves with a F test (see appendix).

The predictive performances of the computer-controlled infusion systems for alfentanil and propofol were evaluated by examining the performance errors. For each blood sample the performance error[20–22] was calculated as $((C_m - C_p)/C_p) \times 100$, where C_m and C_p = the measured and predicted concentrations, respectively, of alfentanil or propofol. Subsequently, the bias and inaccuracy of each system were assessed by determination of the median performance error (MDPE) and the median absolute performance error (MDAPE), and the corresponding 95% confidence intervals. When the 95% confidence interval of the MDPE included zero, it was concluded that no significant bias had occurred. To evaluate whether time affected the accuracy in each of the computer-controlled infusion devices, the performance error and absolute value of the performance error at skin incision and skin closure were compared using the paired *t* test. The performance of the alfentanil and the propofol infusion devices were compared among the three groups by the multisample median test, followed by a multisample comparison test.

Because the results of the deletion-of-*p*'s test showed a linear relation *versus* time, the postoperative time course in the performance of the deletion-of-*p*'s test was evaluated for each patient by linear regression over the appropriate time intervals. The times from arrival in the recovery room until the patients scored 50% and 90% of their preoperative values were estimated for each patient, and compared among the groups using a one way analysis of variance followed by an unpaired *t* test.

Data are presented as mean ± SD, median and range, or percentage, unless stated otherwise. $P < 0.05$ was considered as the minimum level of statistical significance, except for multiple (triple) comparison tests, where $P < 0.02$ was considered significant.

Results

Age, weight, duration of anesthesia, type of surgical procedure and the percentage of time that all four twitches of the train of four were present, did not differ significantly among the three study groups (table 1). The total alfentanil dose was significantly greater in the

Table 1. Patient Characteristics, Percentage of Time with T_4 Present, Duration of Anesthesia, Total Alfentanil, and Propofol Dosages, in the Patients Who Received Alfentanil as a Supplement to a Target Propofol Concentration of 2 μg/ml (Group A), 4 μg/ml (Group B), or 6 μg/ml (Group C)

	Group A (2 μg/ml)	Group B (4 μg/ml)	Group C (6 μg/ml)
Age (yr)	36 ± 7	33 ± 6	38 ± 6
Weight (kg)	64 ± 5	60 ± 6	62 ± 8
Duration (min)	202 ± 32	157 ± 61	199 ± 54
Alfentanil dose (mg)	16.4 ± 4.3*	4.8 ± 1.4†	3.8 ± 2.5
Propofol dose (mg)	1,043 ± 185	1,574 ± 641	2,882 ± 680
Time with T_4 (%)	59 ± 14	68 ± 12	66 ± 15

Duration = time from induction until extubation; T_4 = fourth twitch of the train of four.

* $P < 0.02$ *versus* group B and group C.

† $P < 0.02$ *versus* group A and group C.

patients of group A compared with those of group B and C ($P < 0.02$), and also greater in group B than in group C ($P < 0.02$) (table 1).

None of the patients from group A, 2 patients from group B, and all patients from group C lost consciousness with the initial target alfentanil concentration of 50 ng/ml. In the patients that remained conscious with the initial target alfentanil concentration, unconsciousness was induced when the target alfentanil concentration was increased by 100–200 ng/ml.

The EC_{50} of alfentanil for laryngoscopy, intubation, and the opening of the peritoneum decreased with increasing propofol concentrations (fig. 1). For laryngoscopy, intubation and the opening of the peritoneum the data were best characterized by a concave-up fitted curve (table 2). As blood propofol concentrations increased from 2 to 10 μg/ml, the EC_{50} of alfentanil decreased from 170 to 25 ng/ml for laryngoscopy, from 280 to 23 ng/ml for intubation, and from 259 to 9 ng/ml for the opening of the peritoneum. For skin incision no consistent data set was obtained, the propofol–alfentanil interaction for this stimulus could therefore not be determined.

The number and type of responses that were noted during the intraabdominal part of surgery are presented in table 3. The measured blood propofol concentration remained fairly stable throughout the surgical procedure in all patients (fig. 2). The alfentanil concentration–effect relations in the individual patients of the three groups for the intraabdominal part of the surgical procedure are shown in figures 3–5. In one patient of group B (patient 5) no response was observed during

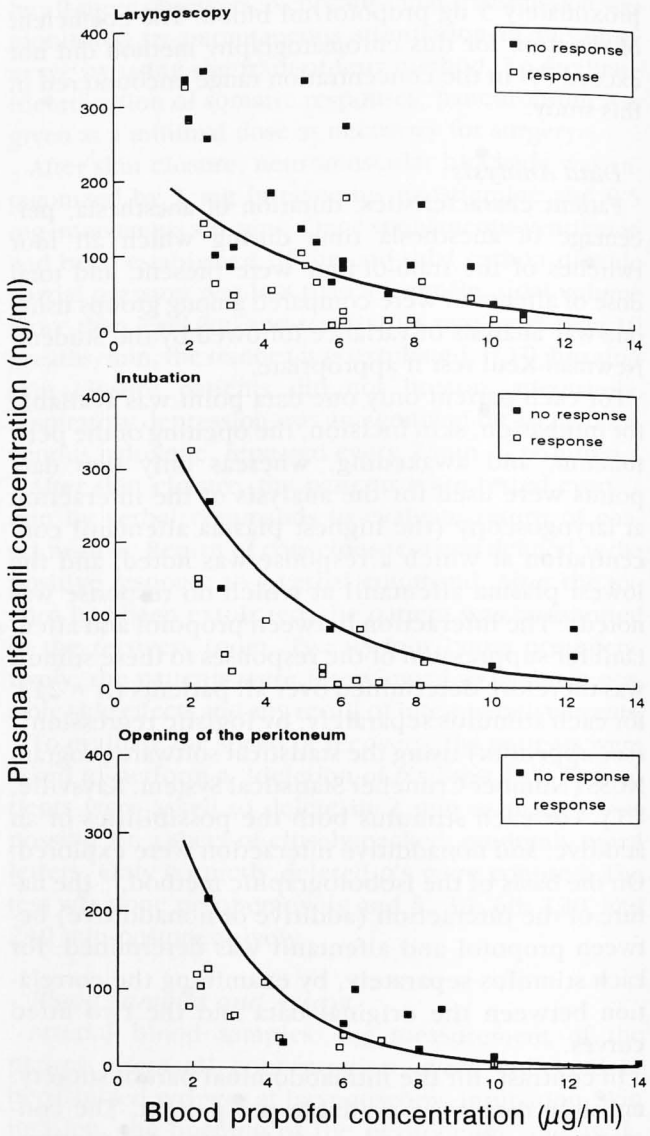

Fig. 1. The concentration–effect relations of the combination of propofol and alfentanil for laryngoscopy, intubation, and opening of the peritoneum. The curves were obtained by logistic regression of the response–no-response data *versus* the corresponding measured blood propofol concentrations and the corresponding natural logarithm of the measured plasma alfentanil concentrations for the three stimuli separately. The displayed curves represent alfentanil and propofol concentrations associated with a 50% probability of no response. Because laryngoscopy was performed more than once, the highest alfentanil concentration associated with a response and the lowest alfentanil concentration without a response were used in the regression. The curve for laryngoscopy is described by the equation: EC_{50} of alfentanil = $e^{(5.588788 - 0.2256.Cprop)}$, where C_{prop} = the blood propofol concentration; $R^2 = 0.27$. The curve for intubation is described by the equation: EC_{50} of alfentanil = $e^{(6.279797 - 0.31562.Cprop)}$; $R^2 = 0.41$. The curve for the opening of the peritoneum is described by the equation: EC_{50} of alfentanil = $e^{(6.412278 - 0.42692.Cprop)}$; $R^2 = 0.38$.

Table 2. The Fitted Values of the Coefficients ± Standard Error (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 Suppression of Responses to Laryngoscopy, Intubation, the Opening of the Peritoneum, and for Awakening, and Their Correlation Coefficients

	$\beta_0 \pm$ SE	$\beta_1 \pm$ SE	$\beta_2 \pm$ SE	R^2
Laryngoscopy*	2.6755 ± 1.2601	−0.2332 ± 0.1465	−0.0122 ± 0.0048	0.18
Laryngoscopy†	9.6845 ± 3.4447	−1.7328 ± 0.5899	−0.3909 ± 0.1891	0.27
Intubation*	6.2789 ± 2.5635	−0.6314 ± 0.3068	−0.0185 ± 0.0090	0.32
Intubation†	17.3504 ± 10.3836	−2.7629 ± 1.7685	−0.8720 ± 0.5076	0.41
Peritoneum opening*	7.3489 ± 3.0877	−0.8464 ± 0.3494	−0.0325 ± 0.0179	0.36
Peritoneum opening†	17.8432 ± 8.7560	−2.7827 ± 1.5130	−1.1880 ± 0.5368	0.38
Awakening*	11.3519 ± 3.6221	−2.9504 ± 0.9422	−0.0709 ± 0.0252	0.45
Awakening†	17.1923 ± 5.4479	−3.0289 ± 0.9401	−2.6782 ± 0.9198	0.47

* β_0, β_1, β_2, and R^2 of the function; EC_{50} of alfentanil = $(-\beta_2 \cdot C_{propofol} - \beta_0)/\beta_1$, exploring the possibility of an additive interaction.

† β_0, β_1, β_2, and R^2 of the function; EC_{50} of alfentanil = $e^{\frac{[(C_{prop} \cdot -\beta_2) - \beta_0]}{\beta_1}}$, exploring the possibility of a nonadditive interaction.

the intraabdominal part of surgery, even though the plasma alfentanil concentration had decreased to 16 ng/ml. The concentration–effect relation of alfentanil for intraabdominal stimuli could therefore not be determined in this patient. The mean blood propofol concentration in this patient was 7.5 μg/ml. In another patient of group B (patient 1) no overlap was found between response and no-response data. In this patient, the EC_{50} was therefore determined as the midrange between the lowest measured plasma alfentanil concentration at which no response occurred and the highest plasma alfentanil concentration at which a response was noted. The EC_{50} of alfentanil *versus* mean blood propofol concentration relation for the intraabdominal part of surgery as determined over all patients, is presented in table 4, and figure 6. The residual sum of squares of the model exploring a nonadditive interaction between propofol and alfentanil was significantly smaller than the residual sum of squares of the model exploring a possible additive interaction (20,009.5 *versus* 36,160.6, respectively; $P < 0.001$). According to the isobolographic method[19] (see appendix), the interaction between propofol and alfentanil was then judged to be synergistic for the suppression of responses to lower abdominal surgery. As the mean blood propofol concentration increased from 2 to 10 μg/ml, the EC_{50} of alfentanil for intraabdominal stimuli decreased from 209 to 16 ng/ml.

Table 3. Type and Number of Responses Observed during the Intraabdominal Part of Surgery in the Patients Receiving Alfentanil as a Supplement to Propofol 2 μg/ml (Group A), 4 μg/ml (Group B), or 6 μg/ml (Group C)

Response Type	Group A (n)	Group B (n)	Group C (n)
Blood pressure*	37	17	28
Blood pressure and pulse	2	2	1
Blood pressure and movement	5	0	0
Movement	2	0	0
Pulse and movement	0	1	0
Autonomic response	1	1	0
Total	47	21	29

* Blood pressure responses were observed in all patients.

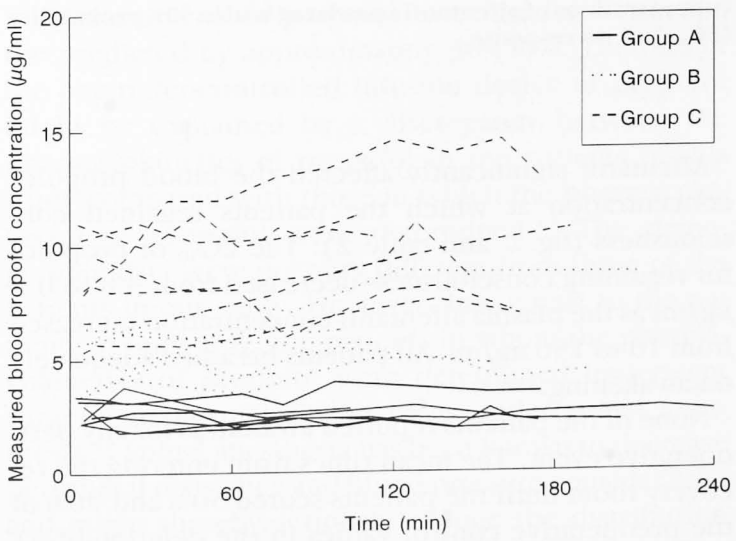

Fig. 2. Measured blood propofol concentrations *versus* time in the individual patients of group A (target propofol concentration 2 μg/ml), group B (target propofol concentration 4 μg/ml), and group C (target propofol concentration 6 μg/ml).

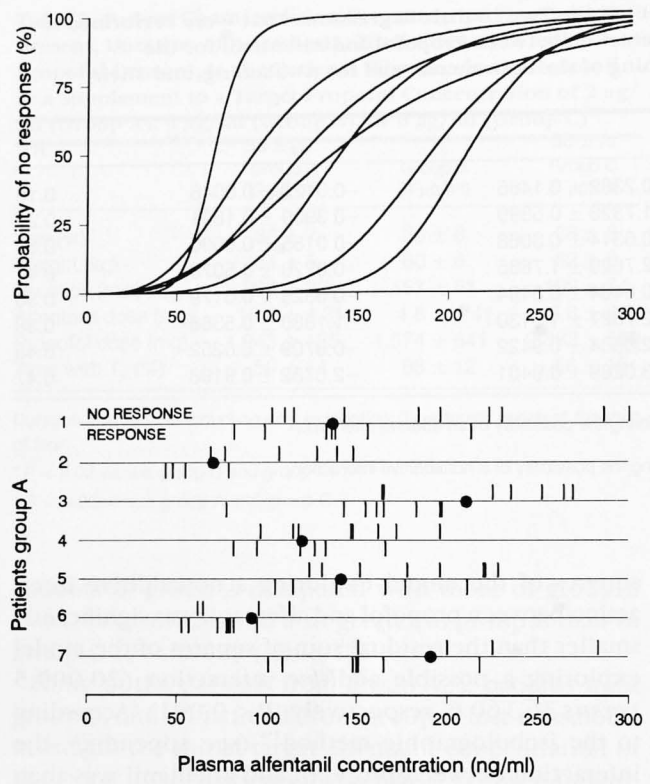

Fig. 3. The alfentanil concentration–effect relations in the individual patients for the intraabdominal part of surgery when alfentanil was given as a supplement to a target propofol concentration of 2 μg/ml. The mean measured blood propofol concentrations were 2.5, 2.8, 2.0, 2.7, 2.6, 3.4, and 2.9 μg/ml in patients 1–7, respectively (see table 4). The curves were determined by logistic regression of response–no-response data *versus* the corresponding measured plasma alfentanil concentrations, as shown beneath the curves. Filled circles = concentrations of alfentanil associated with a 50% probability (EC_{50}s) of no response.

Alfentanil significantly affected the blood propofol concentration at which the patients regained consciousness (fig. 7 and table 2). The EC_{50} of propofol for regaining consciousness decreased from 3.8 to 0.8 μg/ml as the plasma alfentanil concentration increased from 10 to 150 ng/ml. All patients breathed adequately on awakening.

None of the patients reported awareness for any perioperative event. The mean times from entering the recovery room until the patients scored 50% and 90% of the preoperative control values in the deletion-of-*p*'s test, were 79 ± 49 min and 223 ± 53 min for the patients of group A, 105 ± 47 min and 220 ± 49 min in the patients of group B, and 128 ± 48 min and 250 ± 55 min in group C. These were not significantly different among the three groups.

The predictive performance of the computer-controlled infusion device, implemented with alfentanil pharmacokinetic data, did not differ among the three study groups. The median (range) number of blood samples that were taken from each patient for alfentanil determination was 23 (12–32). The MDPE (25th–75th percentiles) and MDAPE (25th–75th percentiles) of

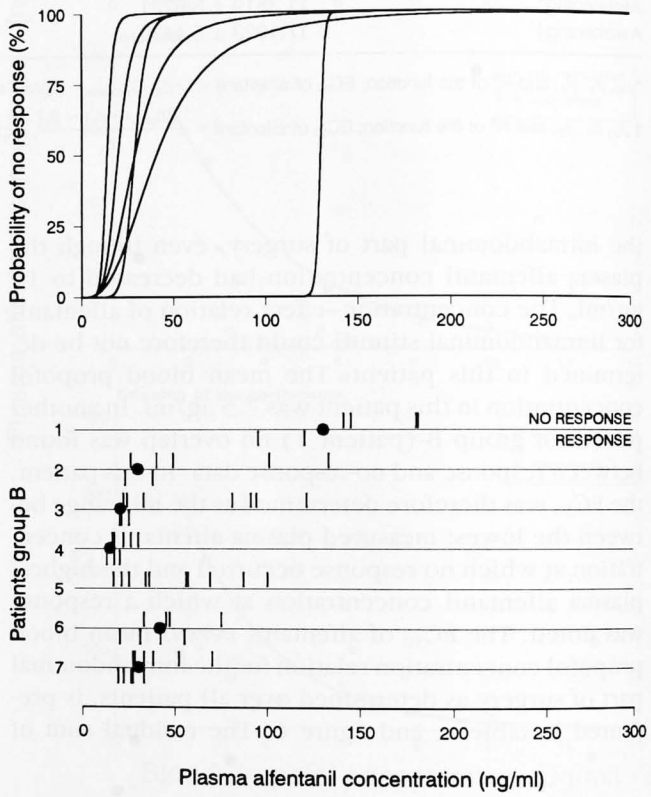

Fig. 4. The alfentanil concentration–effect relations in the individual patients for the intraabdominal part of surgery when alfentanil was given as a supplement to a target propofol concentration of 4 μg/ml. The mean measured blood propofol concentrations were 5.1, 4.4, 5.1, 4.4, 7.5, 5.6, and 6.3 μg/ml in patients 1–7, respectively (see table 4). The curves were determined by logistic regression of response–no-response data *versus* the corresponding measured plasma alfentanil concentrations, as shown beneath the curves. In patient 1, there was no overlap between response and no-response data; in this patient, the alfentanil concentration associated with a 50% probability of no response was determined by the midrange between the highest plasma alfentanil concentration with a response and the lowest plasma alfentanil concentration without a response. In patient 5, no responses occurred, and therefore in this patient the concentration–response relation could therefore not be determined. Filled circles = concentrations of alfentanil associated with a 50% probability (EC_{50}s) of no response.

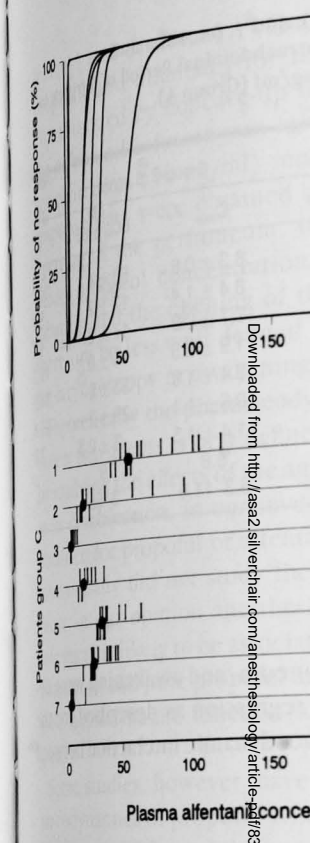

Fig. 5. The alfentanil concentration–e
dividual patients for the intraabdomi
alfentanil was given as a supplement
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the alfentanil infusion system
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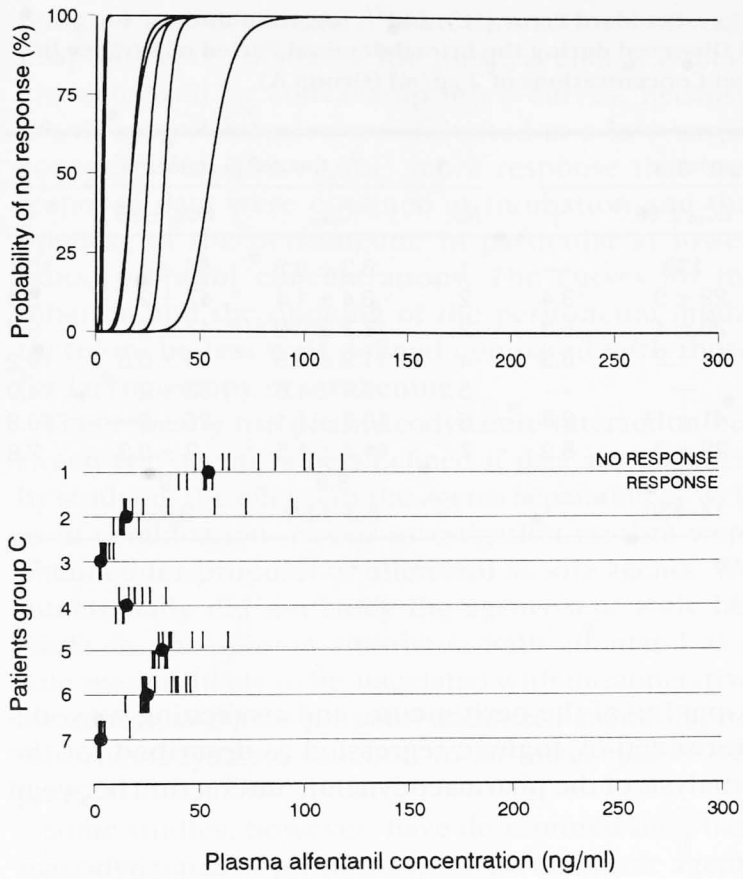

Fig. 5. The alfentanil concentration–effect relations in the individual patients for the intraabdominal part of surgery when alfentanil was given as a supplement to a target propofol concentration of 6 μg/ml. The mean measured blood propofol concentrations were 6.3, 8.4, 11.9, 7.7, 8.4, 10.6, and 11.4 μg/ml in patients 1–7, respectively (see table 4). The curves were determined by logistic regression of response–no-response data *versus* the corresponding measured plasma alfentanil concentrations, as shown beneath the curves. Filled circles = concentrations of alfentanil associated with a 50% probability (EC_{50}s) of no response.

the alfentanil infusion system were −29% (−40–−16%) and 30% (18–41%) in group A, −34% (−46–−12%) and 40% (20–49%) in group B, and −36% (−46–−11%) and 39% (26–52%) respectively, in group C. The MDPE (25th–75th percentiles) and MDAPE (25th–75th percentiles) of the alfentanil computer-controlled infusion device calculated from the data of the combined groups were −33% (−45–−18%) and 34% (21–46%).

The predictive performance of the computer-controlled infusion device, implemented with propofol pharmacokinetic data, did not differ among the three study groups. The median number of blood samples that were taken for propofol determination from each patient was 10 (5–13). The performance error *versus* time of the computer-controlled infusion of propofol in the individual patients is displayed in figure 8. The MDPE (25th–75th percentiles) and MDAPE (25th–75th percentiles) of the propofol infusion system were 30% (11–40%) and 31% (15–43%) in group A, 43% (18–61%) and 43% (18–61%) in group B, and 52% (28–83%) and 52% (28–83%) respectively, in group C. The MDPE (25th–75th percentiles) and MDAPE (25th–75th percentiles) of the propofol computer-controlled infusion device, calculated for the combined data, were 38% (18–65%) and 40% (19–65%). All computer-controlled infusion devices showed a significant bias. No significant difference was found between the performance errors or absolute value of the performance errors at the times of skin incision and skin closure with any of the computer-controlled infusion devices.

Discussion

The main goal of this study was to characterize the pharmacodynamic interaction between propofol and alfentanil with respect to the suppression of responses to several clinically relevant stimuli. The interaction between these agents can only be determined accurately when data are obtained after blood-effect site equilibration of both propofol and alfentanil, and when the blood propofol concentration remains constant during the study. Blood propofol concentrations were fairly stable throughout the surgical procedure in all patients (figs. 2 and 8), although the computer-controlled infusion of propofol showed a significant bias. The measured blood propofol concentrations exceeded the predicted by approximately 30–50%. The bias of the computer-controlled infusion device of propofol might be explained by a discrepancy between the pharmacokinetics of propofol in the patients in this study compared with those in which the pharmacokinetics of propofol were determined.[13] The demographic data were not very different from those of the patients in our study. However, in contrast to the patients in our study, the patients in whom the pharmacokinetics of propofol were determined underwent surgery in the majority of cases under spinal anesthesia.[13] Spinal anesthesia has been known to decrease peripheral resistance and blood pressure considerably, and might thereby seriously change the distribution and elimination of propofol in and from the body. Furthermore, the hemodynamic effects caused by the administration of alfentanil and of propofol itself in the

Table 4. Mean (±SD) Measured Blood Propofol Concentrations, EC_{50} ± Standard Error (SE), and γ, for Alfentanil, Characterizing the Probability of No Response to Surgical Stimuli Observed during the Intraabdominal Period of Surgery in Patients Receiving Alfentanil as a Supplement to Propofol at Target Concentrations of 2 μg/ml (Group A), 4 μg/ml (Group B), or 6 μ/ml (Group C)

Group A (2 μg/ml)				Group B (4 μg/ml)				Group C (6 μg/ml)			
No.	C_{prop}	EC_{50} ± SE	γ	No.	C_{prop}	EC_{50} ± SE	γ	No.	C_{prop}	EC_{50} ± SE	γ
1	2.5 ± 0.5	136 ± 27	2.8	1	5.1 ± 0.6	130	—	1	6.3 ± 0.8	55 ± 4	10.1
2	2.8 ± 0.5	70 ± 9	8.6	2	4.4 ± 0.9	29 ± 9	3.4	2	8.4 ± 1.4	17 ± 2	5.4
3	2.0 ± 0.4	210 ± 14	9.3	3	5.1 ± 0.8	20 ± 4	5.3	3	7.7 ± 0.9	17 ± 2	6.7
4	2.7 ± 0.4	119 ± 21	3.5	4	4.4 ± 0.7	14 ± 2	8.3	4	11.9 ± 2.5	4 ± 0.3	19.2
5	2.6 ± 0.2	140 ± 19	5.1	5	7.5 ± 1.1	—	—	5	8.4 ± 1.6	33 ± 2	14.9
6	3.4 ± 0.4	92 ± 19	3.4	6	5.6 ± 0.8	41 ± 11	2.8	6	10.6 ± 1.1	25 ± 2	10.8
7	2.9 ± 0.3	190 ± 25	6.4	7	6.3 ± 0.7	29 ± 3	8.9	7	11.4 ± 1.5	3 ± 0.3	7.8
Mean*	2.6	121			5.3	27			8.8	9	
Range	2.0–3.4	70–210			4.4–7.5	14–130			6.3–11.9	3–55	

* Harmonic mean.

patients in our study might contribute as well to the described bias.

The pharmacodynamic interactions between propofol and alfentanil for laryngoscopy, intubation, the opening of the peritoneum, and awakening were determined by logistic regression as described for the analysis of the pharmacodynamic interaction between

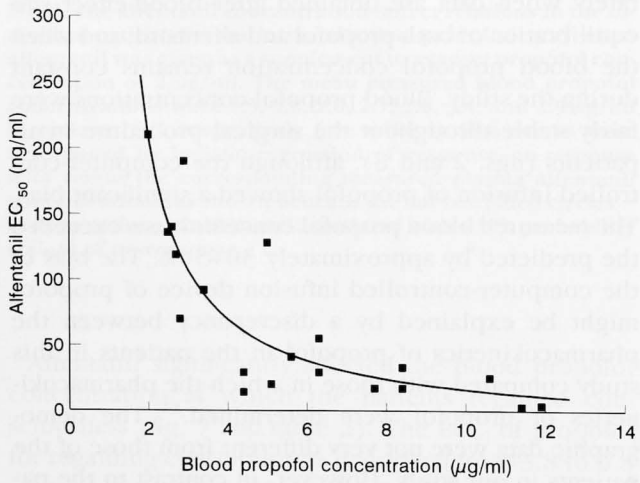

Fig. 6. Plasma alfentanil concentrations *versus* blood propofol concentrations associated with a 50% probability of no response to intraabdominal surgical stimuli. The curve represents a mechanistic function (see appendix) fitted to the data by unweighted least-squares nonlinear regression analysis and is described by the equation: $C_{alf} = (-329.971 \times [21{,}794.8 - \overline{C_{prop}}])/(21{,}794.8 - 26.5 \times \overline{C_{prop}})$, where $\overline{C_{prop}}$ = the mean blood propofol concentration calculated in each patient; $R^2 = 0.74$. Squares = EC_{50}s of alfentanil at corresponding mean blood propofol concentrations for suppression of responses to intraabdominal surgical stimuli as determined in the individual patients by logistic regression (see figs. 3–5).

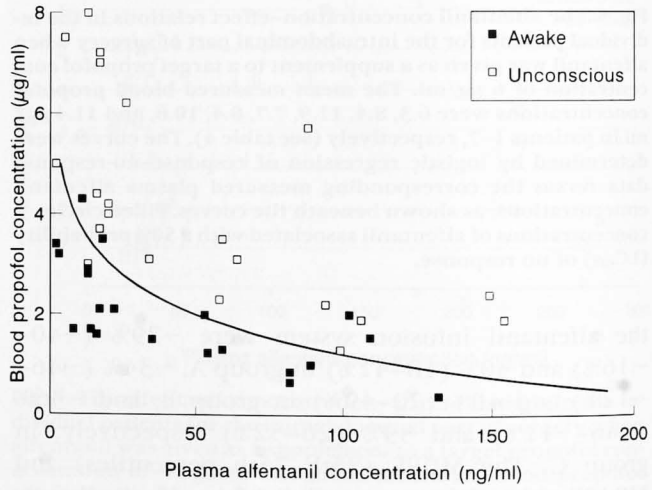

Fig. 7. The concentration–response relation of the combination of propofol and alfentanil for regaining consciousness. The curve was obtained by logistic regression of the awake–unconscious data *versus* the corresponding measured blood propofol concentrations and the corresponding natural logarithm of the measured plasma alfentanil concentrations. Open squares = lowest concentrations of propofol and alfentanil at which the individual patients were still unconscious; filled squares = concentrations of propofol and alfentanil at which the patients regained consciousness. The curve represents the propofol and alfentanil concentration combinations associated with a 50% probability of regaining consciousness and is described by the equation: EC_{50} of propofol = 6.4194 − 1.1310 × Ln C_{alf}; $R^2 = 0.47$.

fentanyl and desflurane.[18] The interaction between propofol and alfentanil for these events was best characterized by concave-up fitted curves. Because the alfentanil infusion was initiated at a low target concentration (50 ng/ml) more response than no-response data were obtained at intubation and the opening of the peritoneum, in particular at lower blood propofol concentrations. The curves for intubation and the opening of the peritoneum might therefore be less well defined compared with those for laryngoscopy or awakening.

Theoretically the pharmacodynamic interaction between two agents is best defined if data are obtained by studying the effects of the agents separately as well as in combination. In our investigation no data were obtained for propofol or alfentanil as sole agents. We intentionally did not study the agents separately because in our opinion anesthesia with alfentanil as a sole agent is likely to be associated with intraoperative awareness, and pure propofol anesthesia may compromise hemodynamic function to an unacceptable degree.

Some studies, however, have determined the pharmacodynamics of propofol when given as sole agent. The reported EC_{50} and the concentration effective in 90% of subjects for induction of loss of consciousness (EC_{90}) are 3.4 and 4.3 μg/ml, respectively, in nonpremedicated patients,[9] and these were not influenced by the concomitant use of fentanyl.# The EC_{50} for skin incision with propofol was reported to be 16 μg/ml, and was reduced by 50% with 0.6 ng/ml fentanyl.# Intraoperatively, blood propofol concentrations of 9–10 μg/ml were necessary for adequate anesthesia during lower abdominal and orthopedic surgery,[23] when no adjuvant analgesics were given. The mean alfentanil EC_{50} for lower abdominal surgery when given as a supplement to propofol anesthesia at a mean blood propofol concentration of 4 μg/ml was defined at 68 ± 37 ng/ml.[10] These data closely correspond to those in this study. With blood propofol concentrations exceeding 10–12 μg/ml very little alfentanil was needed to suppress responses to perioperative stimuli. The fitted curve for the suppression of responses to intraabdominal surgery crosses the X-axis at a blood propofol concentration of 21.8 μg/ml, whereas it never crosses the Y-axis, but lies asymptotically to a line that crosses the X-axis at a blood propofol concentration of 0.8 μg/ml. This suggests that propofol in the absence of alfentanil provides adequate anesthesia, and might therefore be called a complete anesthetic, whereas alfentanil apparently is not capable of replacing propofol completely, and therefore is not to be considered a complete anesthetic. In an analogous finding, Hall *et al.* has found that alfentanil in dogs was capable of decreasing the enflurane minimum alveolar concentration in dogs by only as much as 70%.[24]

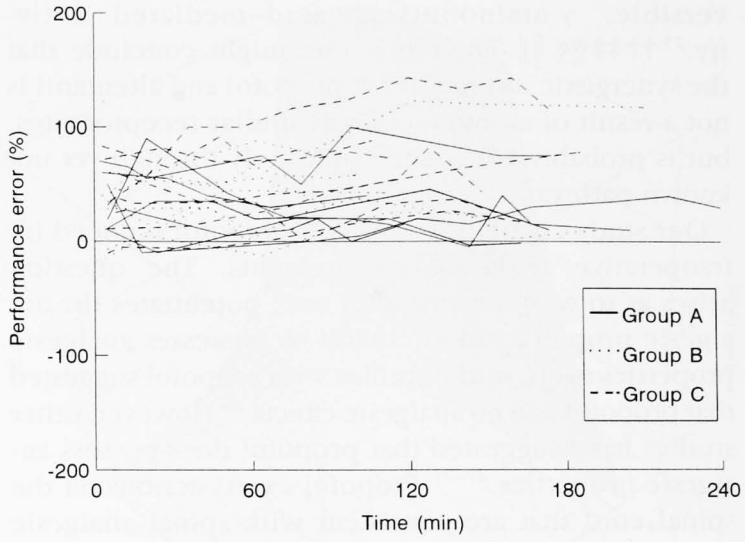

Fig. 8. Performance error *versus* time for the computer-controlled infusion of propofol in the individual patients of group A (target propofol concentration 2 μg/ml), group B (target propofol concentration 4 μg/ml), and group C (target propofol concentration 6 μg/ml).

We conclude that with blood propofol concentrations exceeding 4.3 μg/ml, alfentanil is supplemented predominantly for its analgesic properties because at these propofol concentrations unconsciousness is ensured in the majority of patients (4.3 μg/ml is the concentration of propofol effective in producing loss of consciousness in 90% of subjects[9]). At blood propofol concentrations less than 4.3 μg/ml however, alfentanil is not only required because of its analgesic properties, but because of its sedative properties as well. With blood propofol concentrations less than 0.8 μg/ml adequate anesthesia can not be assured, even in the presence of high plasma alfentanil concentrations.

The synergistic type of interaction between propofol and alfentanil when given for suppression of responses to intraabdominal surgical stimuli may reflect an interaction at similar effector sites or an indirect interaction through separate pathways. The effects of alfentanil are caused by interaction with opioid receptors. Studies suggest that propofol has a dose-related, re-

versible, γ-aminobutyric acid–mediated activity.[25,††,‡‡,§§,‖‖] Therefore, one might conclude that the synergistic interaction of propofol and alfentanil is not a result of an interaction at similar receptor sites, but is probably effectuated indirectly through yet unknown pathways.

Our study clearly showed that propofol reduced intraoperative analgesic requirements. The question arises as to whether propofol only potentiates the analgesic properties of alfentanil or possesses analgesic properties itself. Initial studies with propofol suggested that propofol had no analgesic effects.[26] However, other studies have suggested that propofol does possess analgesic properties.[27–29] Propofol exerts actions on the spinal cord that are consistent with spinal analgesic effects.[30] This effect is attributable, at least in part, to actions that increase the effectiveness of γ-aminobutyric acid A receptors. Some studies suggest that subhypnotic doses of propofol (0.25–0.5 mg/kg) reduce the sensitivity to somatic pain,[28] and decrease the acute pain evoked by argon laser stimulation.[29] Other studies, however, have concluded that propofol only reduces nociception at concentrations that also exert anesthetic effects.[30] Thus, if one defines "pain" as the subjective conscious perception of nociception, it remains yet uncertain whether propofol exhibits analgesic effects. From our study it is clear that propofol undoubtedly reduces nociception to perioperative stimuli in the unconscious patient. We agree with Jewett *et al.*[30] that the overlap between blood propofol concentrations that suppress nociception, cause sedation, and that are required to induce and maintain general anesthesia, may contribute to the reputation of propofol as an agent with only minor analgesic properties.

To gain insight into the sedative and analgesic properties of different anesthetic agents, and to increase the comparability of the effects of different agents, we suggest to index these drugs with respect to their sedative and analgesic properties by calculating the hypnotic–analgesic ratio for each anesthetic agent. This ratio can be determined as the EC_{50} for loss of consciousness (as a parameter of the sedative properties) divided by the EC_{50} for skin incision (as a parameter of the antinociceptive properties). The hypnotic–analgesic ratio for propofol for example, is then calculated[9,#] as 3.4 $\mu g \cdot ml^{-1}/16\ \mu g \cdot ml^{-1} = 0.21$. For thiopental the hypnotic–analgesic ratio is determined[31,32] as 15.6 $\mu g \cdot ml^{-1}/40.5\ \mu g/ml = 0.39$. For inhalational anesthetic agents[1] the hypnotic–analgesic ratio is approximately 0.7, whereas for alfentanil it approaches 1.[33] In contrast to inhalational agents, the slopes of the curves of various intravenous agents are dissimilar. One should therefore keep in mind that for intravenous anesthetic agents the EC_{95} is not a constant multiplication of the EC_{50}, as for the inhalational agents (for inhalational agents ED_{95} is approximately $1.3 \times ED_{50}$[1]).

Finally, we found a strong relation between the plasma alfentanil concentration and the blood propofol concentration at which patients regained consciousness. To date, a large discrepancy exists between the blood propofol concentrations that cause loss of consciousness[9] (EC_{50} 3.4 μg/ml) compared with the blood propofol concentrations at which patients have been reported to regain consciousness after propofol–opioid anesthesia (1–1.5 μg/ml[34]). Hysteresis might partially explain this phenomenon, because the blood propofol and plasma alfentanil concentrations that were taken at awakening[34] were not in equilibrium with the effect site. The blood-effect site equilibration half lives of propofol and alfentanil, however (2.9 min,** and 1.1 min[35] respectively), are very short. The blood propofol and plasma alfentanil concentrations therefore only slightly lag behind those at the effect site after termination of the infusion. Hysteresis can thus not explain the mentioned discrepancy fully. In our study, some patients already regained consciousness at blood propofol concentrations of approximately 4 μg/ml, when alfentanil concentrations were very low. In contrast, with plasma alfentanil concentrations as high as 130 ng/ml, the blood propofol concentration had to decrease to 0.5 − 1 μg/ml before patients regained consciousness. Consequently, we conclude that when the opioid concentration is taken into consideration no discrepancy exists between blood propofol concentrations at loss of consciousness and awakening.

This reasoning could as well explain why no difference was found in the speed of recovery as tested by

†† Yamamura T, Ohtsuka H, Furumido H, Tsutahara S, Kemmotsu O: Does propofol enhance the GABA-mediated synaptic transmission? (abstract). ANESTHESIOLOGY 75:A588, 1991.

‡‡ Hales TG, Lambert JJ: Modulation of the $GABA_A$ receptor by propofol: Protein or lipid interaction? (abstract). ANESTHESIOLOGY 75: A587, 1991.

§§ Hales TG: Direct activation of $GABA_A$ receptors by propofol may be subunit specific (abstract). ANESTHESIOLOGY 77:A695, 1992.

‖‖ Hara M, Ikemoto Y, Kay Y: Propofol activates the $GABA_A$ receptor–ionophore complex in dissociated hippocampal neurons of the rat (abstract). ANESTHESIOLOGY 77:A696, 1992.

the deletion-of-*p*'s test among the patients of the three groups. The higher plasma alfentanil concentrations that were required in the patients who received low blood propofol concentrations refrained these patients from awakening faster than the patients who received high blood propofol concentrations intraoperatively. This tendency is enhanced by the fact that after termination of the infusion, the plasma alfentanil concentration decreases less rapidly than the blood propofol concentration.

To explore this further, we simulated the decay curves of propofol and alfentanil after termination of a computer-controlled infusion of 180 min, using the pharmacokinetic data sets of propofol and alfentanil that were used in this study. We then found that the simulated propofol concentrations decrease by 50% in 10 min, compared with 40 min for alfentanil. These context-sensitive half-times closely correspond to those described previously.[36] Subsequently, we simulated the regimens of propofol and alfentanil infusions at equianesthetic concentration combinations associated with a 50% probability of no response to lower abdominal surgery (propofol concentrations of 1.5, 2, 2.5, . . . 12 μg/ml corresponding with alfentanil concentrations of 373, 209, 143, . . . 11 ng/ml) (fig. 6). For each propofol and alfentanil concentration combination, we examined the decay in the alfentanil and propofol concentrations after a computer-controlled infusion of 180 min. Finally, we derived the intercept between these simulated decay curves and the propofol–alfentanil concentration curve associated with a 50% probability of regaining consciousness (fig. 7) and recorded the corresponding times elapsed since the cessation of the alfentanil and propofol infusions. This time (the time from the termination of the propofol and alfentanil infusion until the alfentanil and propofol concentrations had decreased to concentrations equal to those at which 50% of patients regain consciousness) was found shortest in the simulations (10 min) (fig. 9) after an infusion of propofol with a concentration of 3.5 μg/ml and a corresponding alfentanil concentration of 85 ng/ml. In other words, after equianesthetic infusion regimens of propofol and alfentanil at various concentration combinations equal to the EC_{50}s for suppression of responses to lower abdominal surgery, patients are likely to wake up the fastest after a propofol infusion at a concentration in blood of 3.5 μg/ml. With higher blood propofol concentrations, propofol delays the time after which patients regain consciousness, whereas with lower propofol concentrations, the higher alfentanil requirements delay recovery after termination of the infusion (fig. 9). Because of the longer context-sensitive half-time of alfentanil compared with propofol,[36] recovery is more affected by an increase in alfentanil dosage compared with propofol. This tendency increases, and gains clinical relevance, with increasing duration of infusion, because the context-sensitive half-time of alfentanil increases more with increasing duration of infusion than that of propofol.[36] These concentrations can be used as a guideline from which the propofol and alfentanil infusion regimens should be adjusted to the requirements of the individ-

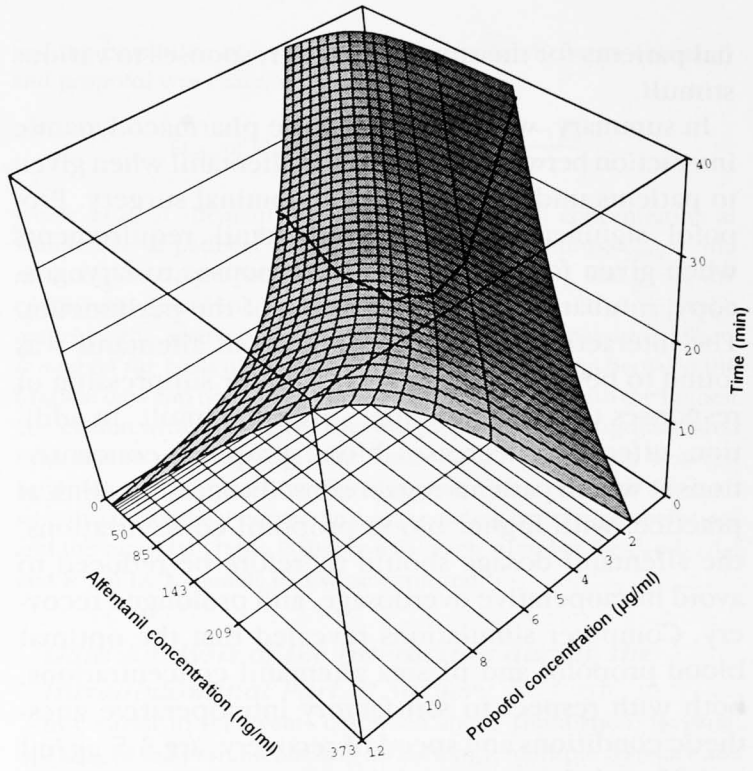

Fig. 9. Computer simulation of the decay in blood propofol and plasma alfentanil concentrations, showing the first 40 min after the termination of a computer-controlled infusion that had been given for 180 min, with target propofol and alfentanil concentrations equal to the alfentanil concentration associated with 50% probability of no response determined for intraabdominal surgery (see fig. 6). The decay curves for propofol and alfentanil were determined with a computer simulation program that was provided with the pharmacokinetic data sets of propofol and alfentanil used in this study.[12,13] Bold line = blood propofol and plasma alfentanil concentrations at which 50% of patients regain consciousness (see fig. 7). The interval between the termination of the infusion of propofol and alfentanil and the time that the propofol and alfentanil concentrations had decreased to concentrations equal to those at which 50% of patients regain consciousness was found to be shortest (10 min) after a 180-min infusion of propofol and alfentanil at concentrations of 3.5 μg/ml and 85 ng/ml, respectively.

ual patients for the suppression of responses to various stimuli.

In summary, we have defined the pharmacodynamic interaction between propofol and alfentanil when given to patients undergoing lower abdominal surgery. Propofol significantly reduces alfentanil requirements when given for suppression of responses to laryngoscopy, intubation, and the opening of the peritoneum. The interaction between propofol and alfentanil was found to be synergistic when given for suppression of responses to intraabdominal surgical stimuli. In addition, alfentanil decreases blood propofol concentrations at which patients regain consciousness. In clinical practice, with higher blood propofol concentrations, the alfentanil dosage should therefore be reduced to avoid intraoperative overdosage, and prolonged recovery. Computer simulations revealed that the optimal blood propofol and plasma alfentanil concentrations, both with respect to satisfactory intraoperative anesthetic conditions and speed of recovery, are 3.5 μg/ml and 85 ng/ml, respectively.

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Appendix

Data Analysis of the Interaction at Laryngoscopy, Intubation, Skin Incision, the Opening of the Peritoneum, and Awakening

For laryngoscopy, intubation, skin incision, the opening of the peritoneum, and awakening, only one or two (laryngoscopy, and awakening) data points were available per patient. Therefore the interaction between propofol and alfentanil for these events was determined over the group (n = 21), by means of a logistic regression using the statistical software program NCSS. The logistic regression models the probability of a dichotomous outcome (yes or no response during one of the above events), as a function of the measured blood propofol and plasma alfentanil concentrations. The logistic regression was performed twice for each stimulus to explore both the possibilities of an additive interaction (a regression of the presence or absence of a response to one of the stimuli *versus* 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 *versus* the measured blood propofol and the *natural logarithm* of the measured plasma alfentanil concentrations).[18] The logistic function is described by the equation:

$$\pi = \frac{e^{\beta_0+\beta_1 x_1+\beta_2 x_2}}{1 + e^{\beta_0+\beta_1 x_1+\beta_2 x_2}}$$

where π = the probability of no response; x_1 = the plasma alfentanil or the natural logarithm of the plasma alfentanil concentration; x_2 = the blood propofol concentration; and β_0, β_1, and β_2 = the coefficients describing the shape of the curve.

The possibility of an additive interaction between alfentanil and propofol was examined by the equation

$$EC_{50} \text{ of alfentanil} = \frac{-\beta_2 \times C_{prop} - \beta_0}{\beta_1}$$

and the possibility of a nonadditive interaction between alfentanil and propofol was examined by the equation

$$EC_{50} \text{ of alfentanil} = e\,\frac{-\beta_2 \times C_{prop} - \beta_0}{\beta_1}$$

where EC_{50} of alfentanil = the plasma alfentanil concentration at which 50% of patients do not respond to the stimulus; C_{prop} = the measured blood propofol concentration; and β_0, β_1, and β_2 are the coefficients describing the shape of the curve. For each stimulus 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. Figure 1 shows for each stimulus the optimal curve, the corresponding correlation coefficient and the raw data. Table 2 displays for each stimulus the β_0, β_1, β_2, and R^2, of both models that were explored.

Data Analysis of the Interaction during the Intraabdominal Part of Surgery

In contrast to the events described above (intubation, incision, opening of the peritoneum, and awakening), multiple response and no-response data were available for each patient for the intraabdominal part of surgery. Therefore, the concentration–effect relation of alfentanil for the suppression of responses to intraabdominal surgical stimuli could be determined in each patient individually. This was done by means of a logistic regression using the statistical software program NCSS. The logistic function is described by the equation:

$$\pi = \frac{e^{\beta_0+\beta_1 x_1}}{1 + e^{\beta_0+\beta_1 x_1}}$$

where π = the probability of no response; x_1 = the measured plasma alfentanil concentration; and β_0 and β_1 = the coefficients describing the shape of the curve. The results of the regression analysis in the individual patients are displayed in figures 3–5 for the patients of the three groups separately. Subsequently, the EC_{50}s of alfentanil for suppression of responses to the intraabdominal surgical stimuli in the individual patients were related to the corresponding mean blood propofol concentrations with a mechanistic model over all patients (n = 21) by unweighted least-squares nonlinear regression analysis. The mechanistic function is described by the equation:

$$\frac{\overline{C_{prop}}}{EC_{50prop}} + \frac{C_{alf}}{EC_{50alf}} + \epsilon \times \frac{\overline{C_{prop}}}{EC_{50prop}} \times \frac{C_{alf}}{EC_{50alf}} = 1,$$

where $\overline{C_{prop}}$ = the mean blood propofol concentration calculated in each patient; C_{alf} = the EC_{50} of alfentanil for suppression of responses to intraabdominal surgical stimuli as determined in each patient by logistic regression; EC_{50prop} and EC_{50alf} = the blood propofol and plasma alfentanil concentrations, respectively, at which 50% of patients do not respond to intraabdominal surgery when these agents are given as sole agents; and ϵ = 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 nonadditive interaction were explored. The possibility of an additive interaction between alfentanil and propofol was examined by the equation

$$C_{alf} = EC_{50alf} - \frac{\overline{C_{prop}} \times EC_{50alf}}{EC_{50prop}}$$

and the possibility of a nonadditive interaction between alfentanil and propofol was examined by the equation

$$C_{alf} = \frac{EC_{50alf} \times (EC_{50prop} - \overline{C_{prop}})}{EC_{50prop} + \epsilon \times \overline{C_{prop}}}.$$

The residual sum of squares of both fitted curves were compared with an F test to determine which fitted line correlated best with the original data. The residual sum of squares of the model exploring a nonadditive interaction between propofol and alfentanil was significantly smaller compared with the residual sum of squares of the model exploring a possible additive interaction (20,009.5 *versus* 36,160.6, respectively; $P < 0.001$). The interaction between propofol and alfentanil for suppression of responses to intraabdominal surgical stimuli is thus best characterized by a nonadditive function. According to the isobolographic method,[19] the interaction between propofol and alfentanil for suppression of responses to intraabdominal surgical stimuli was therefore judged to be synergistic.

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The Effects of Ep
Bupivacaine for
Uteroplacental a

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Background: Ropivacaine is a new
anesthetic that has been shown in an
dysrhythmogenic and cardiotoxic po
The intravenous administration of r
associated with any detrimental effe
in pregnant ewes. The purpose of t
blind study was to examine the effect
for cesarean section on blood flow
uteroplacental and fetal arteries with
and to assess whether the block m
function.

Methods: Healthy parturients wome
plicated pregnancies at term received
vacaine (n = 11) or 0.5% bupivacaine
epidural doses. The first ultrasound
formed before injection of the study
(PI) were derived for the blood flow
the maternal placental and nonplace
placental arcuate artery; and the fe
rebral, and renal arteries. The fetal h
by echocardiography. The PI of the r
and the fetal umbilical artery were r
injection of the local anesthetic. Whe
reached the T6–T4 level, the ultrasou

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