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Pharmacodynamics of Alfentanil as a Supplement to Propofol or Nitrous Oxide for Lower Abdominal Surgery in Female Patients

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Background: **Although propofol and alfentanil are given in combination in clinical practice, the pharmacodynamic interaction between these drugs has not been described.**

Methods: **The pharmacodynamics of alfentanil when given as a supplement to propofol were studied in 10 ASA physical status 1 female patients (group P) undergoing lower abdominal surgery and compared to the pharmacodynamics of alfentanil when given as a supplement to nitrous oxide (group N, n = 10). Anesthesia was induced by either computer-controlled infusion of propofol and alfentanil at target concentrations of 3 μg/ml and 100 ng/ml (group P) or computer-controlled infusion of 400 ng/ml alfentanil as a supplement to nitrous oxide and oxygen (ratio 2:1; group N). The target concentration of alfentanil was varied to patient responses, and the nitrous oxide and propofol concentrations were maintained constant. A sigmoid Emax model was fitted to response/no response data *versus* plasma alfentanil concentrations at intubation, skin incision, and the opening of the peritoneum in both groups and for the intraabdominal part of surgery in the individual patients. In addition, the speed of recovery in both groups was determined by a deletion-of-p's test.**

Results: **The EC_{50} (the concentration at which, with a 50% probability, the patients did not respond to the surgical stimuli) of alfentanil during propofol anesthesia was 92 ng/ml for intubation, 55 ng/ml for skin incision, 84 ng/ml for the opening of the peritoneum, and 66 ± 38 ng/ml (mean ± SD) for the intraabdominal part of surgery. The corresponding values during nitrous oxide anesthesia were significantly higher: 429 ng/ml for intubation, 101 ng/ml for skin incision, and 206 ± 65 ng/ml for the intraabdominal part of surgery ($P < 0.001$). The speed of recovery was similar in both groups.**

Conclusions: **The alfentanil requirements in ASA physical status 1 female patients undergoing lower abdominal surgery are less when given as a supplement to propofol (4 μg/ml) compared to 66% N_2O. (Key words: Analgesics, opioid: alfentanil. Anesthetic techniques: computer-controlled infusion. Anesthetics, intravenous: alfentanil; propofol. Pharmacodynamics: alfentanil; propofol.)**

AS the understanding of the pharmacodynamics of intravenous anesthetic agents improves and as the concentration-response relationships of these agents become better defined, intravenous anesthetics can be administered on a more scientific basis. Especially when computer-controlled infusion techniques are used, well defined pharmacodynamic profiles of intravenous agents enable the clinician to more easily tailor their administration to the needs of each patient. Throughout the intraoperative course, the infusion regimen of these agents then can be based on the concentration-response relationships of the drug for specific surgical stimuli.

The pharmacodynamics of propofol[1–3] and alfentanil[4–7] individually have been studied extensively. Propofol possesses sedative and hypnotic effects, whereas alfentanil mainly acts as an analgesic agent producing only poor sedation at high concentrations. Consequently, in combination, alfentanil and propofol supplement one another and provide satisfactory anesthetic conditions during total intravenous anesthesia for both major and minor surgery.[8,9] Because total intravenous anesthesia with alfentanil and propofol is applied with increasing frequency, and computer-controlled infusion pumps are being used increasingly for this purpose, the characterization of the pharmacodynamic interaction between alfentanil and propofol is gaining clinical relevance. Therefore, we studied the pharmacodynamics of alfentanil when given as a supplement to propofol for lower abdominal surgery in

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ASA physical status 1 female patients and compared those to the pharmacodynamics of alfentanil when given as a supplement to nitrous oxide. In addition, we compared the recovery characteristics of both anesthetic regimens.

Methods and Materials

With approval of the local Medical Ethics Committee and after obtaining informed consent, 20 female patients, ASA 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 of alcohol or smoking more than 10 cigarettes per day also were excluded from the study. The patients were randomly assigned to one of two study groups, receiving either propofol (group P) or nitrous oxide (group N) in combination with alfentanil.

An Atari Portfolio pocket computer (Okasaki, Japan), programmed with three-compartment alfentanil population-based pharmacokinetic data,[4] which were adjusted for patient gender, age, and weight, was used to control an Ohmeda 9000 infusion pump for infusion of alfentanil in all patients. Another Atari pocket computer, programmed with three-compartment propofol pharmacokinetic data,[10] was used to control an Ohmeda 9000 infusion pump for infusion of propofol in the patients of group P.

One hour preoperatively all patients received 10–20 mg oral temazepam as preanesthetic medication. In the operating room, electrocardiography electrodes were attached on the chest, and two electrodes were fixed on the ulnar side of the wrist for monitoring of the neuromuscular function (Myotest®). An intravenous cannula was inserted into a large forearm vein for infusion of alfentanil and propofol, and a cannula was inserted in a radial artery for continuous measurement of arterial blood pressure and collection of blood samples.

After breathing 100% O_2 for 3 min and after 0.02 mg/kg intravenous pancuronium had been given, anesthesia was induced in the patients of group P by computer-controlled infusion of propofol with a target concentration of 3 μg/ml, to be achieved in 2 min. Eight minutes after the start of the propofol infusion, the alfentanil infusion was initiated with a target concentration of 100 ng/ml, to be achieved in 1 min. Fourteen minutes after the start of the propofol infusion, when patients had lost consciousness, 1 mg/kg intravenous succinylcholine was given, and the trachea was intubated.

After breathing 100% O_2 for 3 min and after 0.02 mg/kg intravenous pancuronium had been given, anesthesia was induced in the patients of group N by changing the fresh gas flow to 33% O_2 in 66% N_2O and by starting the computer-controlled infusion of alfentanil with a target concentration of 400 ng/ml, to be achieved in 1 min. Six minutes after the start of the alfentanil infusion, when patients had lost consciousness, 1 mg/kg intravenous succinylcholine was given, and the trachea was intubated.

During the procedure, the lungs of the patients in group P were ventilated with 30% O_2 in air to an end-tidal carbon dioxide concentration of 30–38 mmHg. Similarly the lungs of the patients in group N were ventilated with 33% O_2 in 66% N_2O until skin closure. The propofol infusion was discontinued about 10 min before skin closure.

In both groups, the alfentanil administration was continued and changed in response to signs of inadequate anesthesia. When signs of inadequate anesthesia developed, the target alfentanil concentration was increased by 25–50 ng/ml for 10 min. When no signs of inadequate anesthesia were observed for 10 min, the alfentanil target concentration was decreased by 25–50 ng/ml. The alfentanil infusion was discontinued about 10 min before skin closure.

Inadequate anesthesia was defined by the following criteria:

1. an increase in systolic blood pressure by more than 15 mmHg above normal for that patient (The normal systolic blood pressure was defined as the mean of three systolic blood pressure measured from admission until premedication.)
2. a heart rate exceeding 90 bpm 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 by a resident in anesthesia, an anesthesiologist, and a medical student for evidence of inadequate anesthesia as defined above. If inadequate anesthesia was detected, it was only accepted if verified by all three observers. Neuromuscular transmission was monitored by percutaneous stimulation of the ulnar nerve using

the train-of-four method. To facilitate identification of somatic responses, pancuronium was given at a minimal dose necessary for surgery. After skin closure, residual neuromuscular blockade was antagonized by 1 mg intravenous neostigmine and 0.5 mg intravenous atropine. Once spontaneous ventilation was established, the end-tidal carbon dioxide concentration was less than 6 vol%, tidal volume more than 7 ml/kg, and respiratory rate more than 10 breaths/min, the trachea was extubated. If patients did not breathe adequately 10 min after skin closure, respiratory depression was antagonized by 40 μg intravenous naloxone every 2 min. After extubation, the patient was transported to the recovery room.

To evaluate the speed of recovery, patients were asked to perform a deletion-of-p's test[11,12] preoperatively and 5, 30, 60, 120, and 240 min postoperatively. The patients were asked to delete in 2 min as many p's as possible from a foolscap sheet of closely packed, randomly typed letters. Only correctly deleted p's were counted.

Blood Samples and Assays

Arterial blood samples, for the determination of the plasma alfentanil concentration in the two groups, were collected in heparinized syringes at intubation, skin incision, the opening of the peritoneum, skin closure, and extubation. Samples were also obtained 4 and 10 min after a predicted target alfentanil concentration was achieved during the intraoperative period. In group P, every 20–30 min an additional arterial blood sample was taken in a syringe with potassium oxalate for determination of the blood propofol concentration. The concentrations of alfentanil in plasma were determined by capillary gas chromatography.[5] 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 determined by reversed-phase high-performance liquid chromatography.[3] The coefficient of variation of the high-performance liquid chromatography method did not exceed 7% in the concentration range encountered in this study.

Data Analysis

The sizes of the two study groups were determined on the basis of a power analysis. Ausems *et al.*[6] previously reported that the EC_{50} (the concentration at which, with a 50% probability, the patients did not respond to the surgical stimuli) of alfentanil for the intraabdominal part of lower abdominal surgical procedures was 309 ± 44 ng/ml (mean ± SD), defined in a group of patients comparable to those that participated in our study. The smallest clinically relevant difference in alfentanil requirement between the patients receiving nitrous oxide or propofol was decided to be 25%. With a power of 90% ($\alpha = 0.05$), the group size was determined at 15 patients each. It was decided to perform an interim analysis when 2 times 10 patients had been studied, where $P < 0.025$ was used as a criterion to discontinue the study at that point.

Patient characteristics, duration of anesthesia, percentage of anesthesia time that all four twitches of the train-of-four were present, and total dose of alfentanil were compared between groups using an unpaired *t* test. The number of patients with specific side effects was compared using Fisher's exact test, and the frequency of occurrence of different responses to surgical stimuli by the χ^2 test.

For each patient, a sigmoid Emax model was fitted to the presence or absence of responses during the intraabdominal part of surgery *versus* the corresponding measured plasma alfentanil concentrations. The Sigmoid Emax model is described by the equation:

$$\text{Probability of no response} = \frac{C_p^{\gamma}}{EC_{50}^{\gamma} + C_p^{\gamma}},$$

where C_p is the measured plasma alfentanil concentration, and γ is a dimensionless parameter characterizing the slope of the curve of the concentration-effect relationship. The curve was fitted by unweighted least-squares nonlinear regression analysis using the software package Siphar (Simed, Créteil, France). The presence or absence of a response to intubation, skin incision, and the opening of the peritoneum *versus* the corresponding plasma alfentanil concentrations in each group was evaluated by fitting a sigmoid Emax model as described above after combining the data of the individual patients within each group. The values of the EC_{50} of alfentanil for the intraabdominal part of surgery were compared between groups using an unpaired Student's *t* test.

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[13–15] was calculated as $[(C_m - C_p)/C_p] \times 100$, where C_m and C_p are 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 performance of 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 a paired *t* test.

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 between the two groups with 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.

Results

The size of the two study groups was set at 15 patients per group on the basis of a power analysis using previously described alfentanil pharmacodynamic data for the intraabdominal part of lower abdominal surgery, determined during nitrous oxide anesthesia. Preliminary evaluation after studying 10 patients per group revealed a much larger difference ($P < 0.001$) in alfentanil requirement between the two groups than the preset 25%. Therefore, the study was discontinued and now contains two groups of 10 patients.

Table 1. Patient Characteristics, Type of Surgery, and Duration of Anesthesia in the Patients Who Received Alfentanil as a Supplement to Propofol (Group P)

Patient No.	Age (yr)	Weight (kg)	Surgical Procedure	Duration (min)	Percentage of Time with Detectable T4
P1	35	67	SRRFT	344	57
P2	45	66	HYST	107	30
P3	34	55	SRRFT	298	48
P4	53	60	HYST	119	65
P5	30	50	SRRFT	248	60
P6	43	64	HYST	199	28
P7	42	82	HYST	128	42
P8	28	63	SALP	153	89
P9	41	65	HYST	120	54
P10	41	65	HYST	101	63
Mean	39	65		182	54
SD	7	9		83	17

SRRFT = segmental resection and reanastomosis of the fallopian tube; HYST = abdominal hysterectomy; SALP = salpingostomy with lysis of adhesions and approximation of ovary; Duration = time from induction of anesthesia until extubation; T4 = fourth twitch of the train-of-four.

Table 2. Patient Characteristics, Type of Surgery, and Duration of Anesthesia in the Patients Who Received Alfentanil as a Supplement to Nitrous Oxide (Group N)

Patient No.	Age (yr)	Weight (kg)	Surgical Procedure	Duration (min)	Percentage of Time with Detectable T4
N1	43	83	SRRFT	226	31
N2	36	64	SALP	171	58
N3	31	56	SALP	151	39
N4	45	78	SRRFT	201	50
N5	24	87	SRRFT	240	36
N6	28	71	SRRFT	235	76
N7	39	60	SRRFT	239	45
N8	45	78	HYST	124	70
N9	48	66	HYST	137	68
N10	49	61	HYST	100	49
Mean	39	70		182	52
SD	8	10		50	16

SRRFT = segmental resection and reanastomosis of the fallopian tube; HYST = abdominal hysterectomy; SALP = salpingostomy with lysis of adhesions and approximation of ovary; Duration = time from induction of anesthesia until extubation; T4 = fourth twitch of the train-of-four.

Age, weight, duration of anesthesia, type of surgical procedure, and percentage of time that all four twitches of the train-of-four were present did not differ between the two study groups. These data are presented in tables 1 and 2.

All but one patient in group N lost consciousness within 3 min. In this patient, the target alfentanil concentration had to be increased from 400 to 600 ng/ml to establish unconsciousness. In group P, all patients lost consciousness within 10 min after the start of the propofol infusion. Side effects observed during the induction of anesthesia are shown in table 3. No signif-

Table 3. Type and Frequency of Side Effects Observed during Induction of Anesthesia and Frequency of Postoperative Nausea in Patients Receiving Alfentanil as a Supplement to Propofol (Group P) or Nitrous Oxide (Group N)

Side Effects	Group P (n)	Group N (n)
Muscle rigidity at induction	0	4
Excitation during induction	1	2
Tachycardia at induction	0	1
Bradycardia at induction	2	6
Hypotension during induction	4	1
Postoperative nausea	2	5

icant difference was found in the incidence of any of the side effects between the two groups. Bradycardia and hypotension were treated successfully with 0.25 mg intravenous atropine and a rapid infusion of 200–300 ml of saline, respectively.

The mean alfentanil dose requirement in group P was 10.3 ± 6.1 mg, compared to 22.8 ± 6.4 mg in group N ($P < 0.001$). The mean propofol dose given to the patients of group P was 1393 ± 569 mg. The EC_{50} ± SE (standard error) of alfentanil when given as a supplement to propofol was 92 ± 20 ng/ml for intubation, 55 ± 16 ng/ml for skin incision, and 84 ± 4 ng/ml for the opening of the peritoneum (fig. 1). When given as a supplement to nitrous oxide, the corresponding values were 429 ± 42 ng/ml for intubation and 101 ± 16 ng/ml for skin incision (fig. 2). For the opening of the peritoneum in the patients of group N, no consistent data set was obtained; the EC_{50} for this stimulus, therefore, could not be determined in this group.

The number and type of responses occurring during the intraabdominal part of surgery in the patients of both groups are displayed in table 4. The patients in

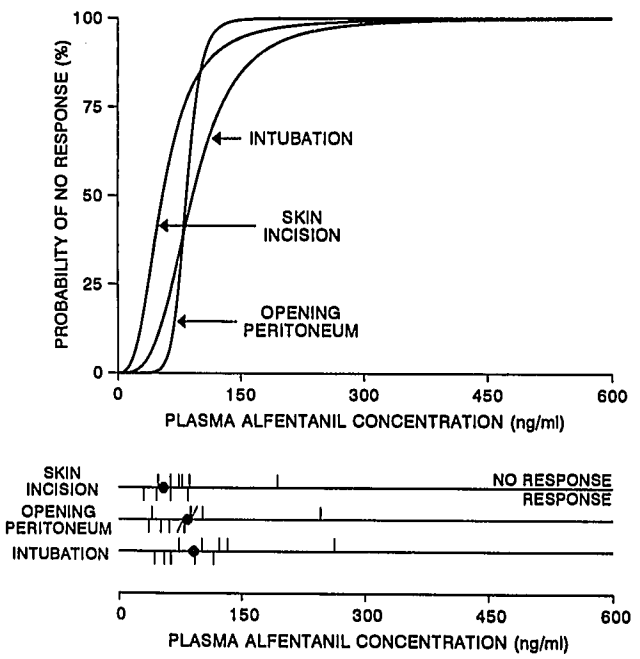

Fig. 1. The alfentanil concentration-effect relationships for intubation, skin incision, and the opening of the peritoneum when given as a supplement to propofol. The curves were determined by fitting a sigmoid Emax model to response/no response data *versus* the corresponding measured plasma alfentanil concentrations, as displayed underneath the curves. Dots represent EC_{50}.

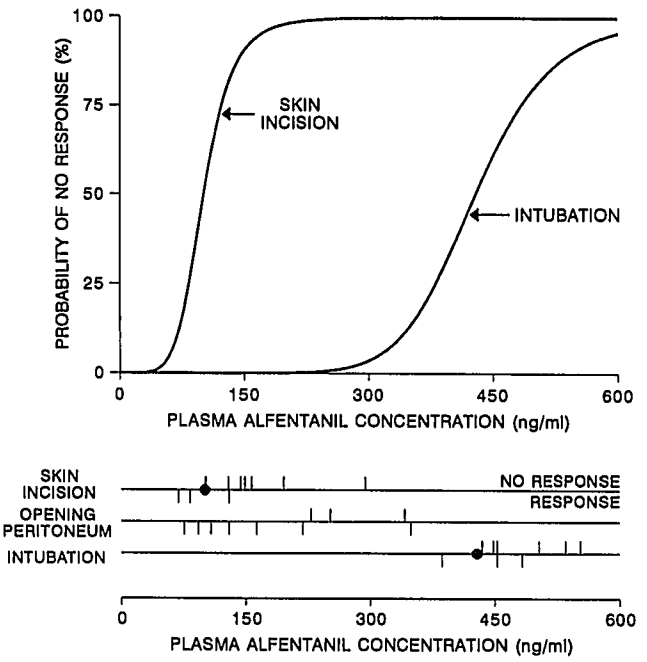

Fig. 2. The alfentanil concentration-effect relationships for intubation and skin incision when given as a supplement to nitrous oxide. The curves were determined by fitting a sigmoid Emax model to response/no response data *versus* the corresponding measured plasma alfentanil concentrations as displayed underneath the curves. Dots represent EC_{50}.

group P more often responded by movement compared to the patients of group N ($P < 0.001$), although the percentage of time at which all four twitches were present did not differ between the patients of both groups.

All responses were controlled rapidly by increasing the target alfentanil concentration. The values of the EC_{50} of alfentanil for the intraabdominal surgical stimuli were significantly lower in the patients of group P

Table 4. Type and Frequency of Responses Observed during the Intraabdominal Part of Surgery in the Patients Receiving Alfentanil as Supplement to Propofol (Group P) or Nitrous Oxide (Group N)

Response Type	Group P (n)	Group N (n)
Blood pressure	23	11
Blood pressure and pulse	2	2
Blood pressure and movement	3	14
Movement	5	12
Pulse and movement	0	1
Autonomic response	0	2
Total	33	42

Table 5. EC_{50} and γ of Alfentanil for the Probability of No Response to Surgical Stimuli during the Intraabdominal Period of Surgery in Patients Receiving Alfentanil as a Supplement to Propofol (Group P) or Nitrous Oxide (Group N)

Group P				Group N		
Patient No.	EC_{50} ± SE (ng/ml)	γ	C_b of P (μg/ml)	Patient No.	EC_{50} ± SE (ng/ml)	γ
P1	112 ± 8	10.8	4.6 ± 1.0	N1	225 ± 33	4.9
P2*	62	—	4.5 ± 0.7	N2	325 ± 10	25.7
P3*	110	—	4.7 ± 1.0	N3*	88	—
P4	11 ± 4	2.1	4.4 ± 0.7	N4	148 ± 13	7.4
P5	27 ± 2	7.9	4.9 ± 1.1	N5	211 ± 25	6.7
P6	124 ± 14	6.7	3.5 ± 0.7	N6	245 ± 14	8.2
P7	66 ± 13	4.5	3.2 ± 0.5	N7	124 ± 17	6.7
P8	67 ± 19	2.9	3.3 ± 0.4	N8	248 ± 38	5.3
P9	64 ± 1	30.0	3.5 ± 0.8	N9	215 ± 64	2.7
P10*	19	—	3.5 ± 0.4	N10	229 ± 48	3.8
Mean	66.2		4.01		205.8	
SD	37.7		0.63		65.2	

C_b of P = mean measured blood propofol concentration.

* In patients P2, P3, P10, and N3 no overlap between response and no response data occurred. In these patients, the EC_{50} was determined by the midrange between the highest plasma alfentanil concentration with a response and the lowest plasma alfentanil concentration without a response.

compared to those in group N: 66.2 ± 37.7 ng/ml *versus* 205.8 ± 65.2 ng/ml ($P < 0.001$; figs. 3 and 4, table 5). The mean measured blood propofol concentration in the patients of group P was 4.0 ± 0.6 μg/ml. The highest mean measured blood propofol concentration was 4.9 μg/ml, the lowest 3.2 μg/ml. No relation was found between the mean measured blood propofol concentrations and the EC_{50} of alfentanil for the intraabdominal part of surgery.

None of the patients in group P and one patient in group N needed naloxone to establish adequate spontaneous respiration according to the described criteria. The mean plasma alfentanil concentration and mean blood propofol concentration at the time of extubation, when the patients breathed 100% O_2, in group P were 44 ± 26 ng/ml and 1.5 ± 0.6 μg/ml, respectively. The plasma alfentanil concentration at the time of extubation in the nine patients in group N who did not need naloxone was significantly higher: 133 ± 51.8 ng/ml ($P < 0.001$). The plasma alfentanil concentration of the patient in group N who needed 0.12 mg intravenous naloxone to restore adequate respiration was 145 ng/ml.

The mean values in the deletion-of-p's test as scored pre- and postoperatively by the patients in both groups are shown in figure 5. The mean times from entering the recovery room until the patients scored 50% and 90% of the preoperative control values were 93 ± 44 min and 204 ± 60 min, respectively, in group P compared to 73 ± 41 min and 205 ± 79 min, respectively, in group N. These were not significantly different between the two groups.

Postoperatively, five patients in group N and two in group P complained of nausea. None of the patients reported awareness during intubation or during any period of the surgical procedure.

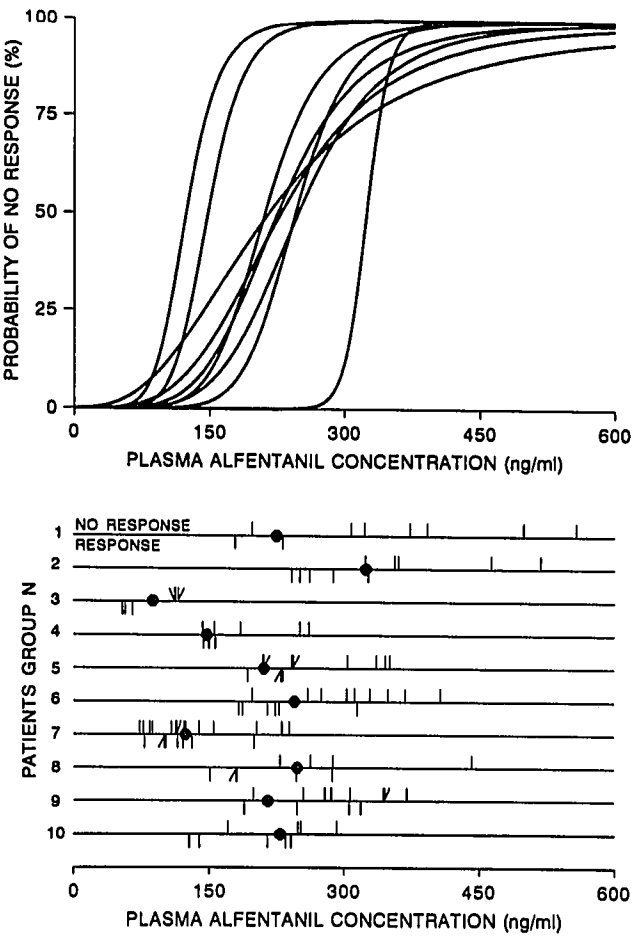

Fig. 3. The alfentanil concentration-effect relationships in the individual patients for the intraabdominal part of surgery when given as a supplement to nitrous oxide. The curves were determined by fitting a sigmoid Emax model to response/no-response data *versus* the corresponding measured plasma alfentanil concentrations as displayed underneath the curves. In patient N3, no overlap between response and no-response data occurred. In this patient, the EC_{50} was determined by the mid range between the highest plasma alfentanil concentration with a response and the lowest plasma alfentanil concentration without a response. Dots represent EC_{50}.

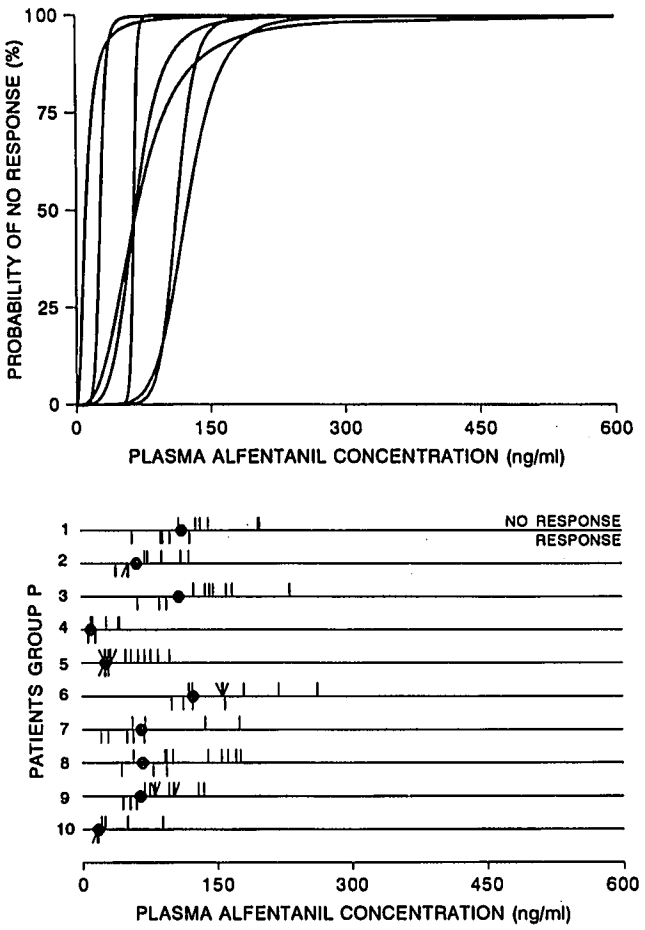

Fig. 4. The alfentanil concentration-effect relationships in the individual patients for the intraabdominal part of surgery when given as a supplement to propofol. The curves were determined by fitting a sigmoid Emax model to response/no-response data *versus* the corresponding measured plasma alfentanil concentrations as displayed underneath the curves. In the patients P2, P3, and P10, no overlap between response and no-response data occurred. In these patients, the EC_{50} was determined by the mid range between the highest plasma alfentanil concentration with a response and the lowest plasma alfentanil concentration without a response. Dots represent EC_{50}.

The predictive performance of the computer-controlled infusion device when implemented with alfentanil pharmacokinetic data did not differ between the two study groups. The MDPE (25^{th}–75^{th} percentile) and MDAPE (25^{th}–75^{th} percentile) of the alfentanil infusion system were −25% (−41–−8%) and 31% (16–44%), respectively, in group P, compared to −19% (−35–0%) and 25% (10–37%), respectively, in group N. The bias (25^{th}–75^{th} percentile) and inaccuracy (25^{th}–75^{th} percentile) of the computer-controlled infusion device when implemented with propofol pharmacokinetic data were 24% (7–60%) and 28% (13–60%), respectively. In group P, 188 blood samples were taken for plasma alfentanil concentration analysis and 95 for blood propofol concentration analysis. In group N, 205 blood samples were drawn for the determination of the plasma alfentanil concentration. All three computer-controlled infusion devices showed a significant bias. No difference was found between the performance errors or absolute value of the performance errors between skin incision and skin closure with any of the computer-controlled infusion devices.

Discussion

The objectives of this investigation were to define the plasma alfentanil concentrations needed to prevent responses to perioperative stimuli during propofol anesthesia and to compare these to the plasma alfentanil concentrations needed in a similar group of patients receiving nitrous oxide anesthesia.

The study was designed such that the concentration-response relationships were determined after propofol and alfentanil had equilibrated between the central compartment and the effect site. The blood-brain equilibration half-life of propofol is approximately 2.9 min.# For this reason, in each patient in group P, the

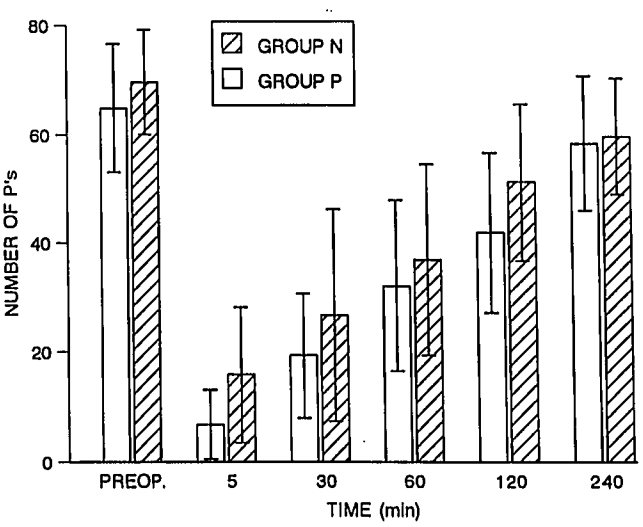

Fig. 5. Mean scores in the deletion-of-p's test as scored preoperatively (PREOP) and 5, 30, 60, 120, and 240 min after entering the recovery room by the patients of both groups. Bars indicate standard deviations.

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trachea was intubated 14 min after the infusion of propofol was started, *i.e.*, after more than four equilibration half-lives. By this time, blood-brain equilibration should be approximately 94% complete. It should be emphasized that, although all patients in group P were unconscious within 10 min after the start of the propofol infusion, the propofol effect site concentration may be increasing after that time. The blood-brain equilibration half-life of alfentanil is approximately 1.1 min.[16] Therefore, blood samples for the determination of the plasma alfentanil concentrations were collected 4 min after any change in target alfentanil concentration, when blood-brain equilibration should be 94% complete. However, some responses occurred while the plasma alfentanil concentration was declining just after the target alfentanil concentration had been decreased, and when presumably blood-brain equilibration was not complete. Computer simulations, using an effect-site equilibration half-life of alfentanil of 1.1 min,[16] suggest that the effect-site alfentanil concentrations would be only 3–6% higher than the measured plasma alfentanil concentrations in these cases.

The alfentanil infusion scheme in group P was based on observations obtained during a pilot study, preceding the present study, in which the EC_{50} for intubation with alfentanil as a supplement to propofol was found to be approximately 100 ng/ml. The alfentanil infusion scheme in group N was based on observations by Ausems *et al.*[6] and Lemmens *et al.*[5]; the initial target alfentanil concentration was equal to the EC_{50} for intubation with alfentanil as described by these authors. The propofol infusion scheme was based on computer simulations of the manual infusion scheme described by Roberts *et al.*,[17] as well as on the concentrations-effect relationships of propofol, as described[3] recently. The target propofol concentration of 3 μg/ml resulted in a mean measured blood propofol concentration in the patients of group P of about 4 μg/ml. This is close to the EC_{90} for loss of consciousness with propofol[3] when given as a sole agent and comparable to the blood propofol concentrations achieved with the manual infusion scheme by Roberts *et al.*[17]

Our study thus describes the pharmacodynamics of alfentanil when given in combination with concentrations of propofol or nitrous oxide that are used in clinical practice. However, apart from this practical aspect, one might question whether the pharmacodynamics of alfentanil were studied during equipotent concentrations of propofol and nitrous oxide.

For inhalation agents, the potency is generally described by the minimal alveolar concentration (MAC). For humans, the MAC is defined as the minimal alveolar concentration (at 1 atmosphere) at which 50% of the patients move in response to surgical incision. Consequently, when comparing the anesthetic potencies of inhalational and intravenous agents, one should compare the MAC of the inhalational agent to the EC_{50} for skin incision of the intravenous agent. For propofol, the EC_{50} for skin incision in unpremedicated patients is 16 μg/ml.[18] For nitrous oxide, the MAC in unpremedicated patients is 105%. Thus, 66% N_2O equals 0.6 MAC and 4 μg/ml propofol equals 0.25 EC_{50} for skin incision. Thus, although premedication in our study may influence the MAC and EC_{50} for skin incision, one would expect to need less alfentanil to obviate perioperative stress responses during nitrous oxide (66%) anesthesia compared to propofol (4 μg/ml). However, we found that the alfentanil requirements during propofol anesthesia were lower than during nitrous oxide anesthesia. Therefore, we conclude that alfentanil combined with propofol exerts a greater synergistic anesthetic effect compared to alfentanil combined with nitrous oxide. Furthermore, we recognize that the pharmacodynamics of alfentanil probably will differ at different blood propofol concentrations. The concentration-effect relationships of alfentanil at different blood propofol concentrations are not yet known.

When intravenous anesthesia is applied, adjuvant dosages of both the sedative agent as well as the analgesic agent can be given to control periods of inadequate anesthesia. We preferred to maintain the target propofol concentration constant and to vary the target alfentanil concentration according to the responses of the patients, and not *vice versa,* for several reasons. First, changing both infusion schemes intraoperatively is not preferable since this might decrease the anesthetic stability and increase the chance of over- and underdosing the patient. Secondly, in our opinion, the required level of unconsciousness does not change during the course of the surgical procedure in contrast to the required level of analgesia. This is stressed by the findings of previous studies,[5–7] and by ours, that show that the intraoperative period is characterized by significant fluctuations in the degree of nociception. Thirdly, since the blood-brain equilibration half-life of alfentanil is shorter compared to propofol, periods of inadequate anesthesia will theoretically be treated faster as these periods are encountered by an increase

in the plasma alfentanil concentration compared to an increase in the blood propofol concentration. However, no consensus on this subject exists. Some anesthetists might decide to change the concentrations of propofol and fix the target alfentanil concentration because, especially after prolonged infusion, the decline in plasma concentration after termination of the infusion is steeper after propofol infusion compared to alfentanil.[19]

Comparing the results of our study to previous studies, we find that the EC_{50} of alfentanil for intubation in the patients receiving nitrous oxide in our study (429 ± 42 ng/ml) is comparable to that described by Lemmens *et al.*[7] (440 ng/ml) and Ausems *et al.*[6] (449 ± 25 ng/ml; mean ± SEM). The average EC_{50} (±SD) of alfentanil for skin incision in our study (101 ± 16 ng/ml) is considerably lower than those of Lemmens *et al.*[7] (226 ng/ml) and Ausems *et al.*[6] (241 ± 16 ng/ml). We have no explanation for this difference. The average EC_{50} (± SD) of alfentanil for the intraabdominal part of surgery in the patients receiving nitrous oxide (206 ± 65 ng/ml) is similar to that described by Lemmens *et al.* (269 ± 97 ng/ml; $P > 0.02$), but smaller than that described by Ausems *et al.*[6] (302 ± 70 ng/ml; $P < 0.05$). Factors that may contribute to this difference include that Ausems *et al.* studied the opening of the peritoneum and the intraabdominal part of surgery as one, whereas we studied the opening of the peritoneum (a stimulus with a relatively high EC_{50}) and the stimuli during the intraabdominal part of surgery separately. Furthermore, differences in patient characteristics, type of surgery, and the interpretation of the criteria of inadequate anesthesia, which is probably consistent within but variable between investigators, might have contributed to this discrepancy as well.

The side effects observed during our study are similar to those previously described.[5–7] The induction of anesthesia in the patients receiving alfentanil as a supplement to nitrous oxide frequently was accompanied by muscle rigidity. In contrast, none of the patients receiving alfentanil as a supplement to propofol showed muscle rigidity. It is likely that the higher initial concentration of alfentanil in group N (400 ng/ml) compared to group P (100 ng/ml) contributed to this difference between the two groups. Also, nitrous oxide is known to aggravate muscle rigidity induced by opioids,[20] whereas a recent study[21] suggests that propofol can prevent and diminish opioid-induced chest wall rigidity. This effect of propofol is analogous to the effect of benzodiazepines and barbiturates that decrease the incidence of muscle rigidity induced by opioids** as well.

The predictive performance of the alfentanil infusion devices was similar in both groups. As previously described,[22] this suggests that the pharmacokinetics of alfentanil are similar when given as a supplement to either propofol or nitrous oxide. The bias of the alfentanil infusion device in our study is approximately −20%. In general, a bias of less than ±30% is acceptable in clinical practice. We therefore conclude that the population-based alfentanil pharmacokinetic data set of Maitre *et al.*[4] is appropriate for use in computer-controlled infusion in ASA physical status 1 female patients. However, as concluded by Raemer *et al.*,[13] the Maitre-pharmacokinetic data set seems inappropriate when used for computer-controlled infusion in the whole population. The predictive performance of the computer-controlled infusion device that was used for the infusion of propofol (MDPE 24%, MDAPE 28%) was comparable to that found in a recent study by us[3] in which propofol was given as single agent (MDPE 26%, MDAPE 27%).

In conclusion, we have defined the pharmacodynamics of alfentanil when given as a supplement to propofol (4 μg/ml) and compared these to the pharmacodynamics of alfentanil when given as a supplement to nitrous oxide (66%) in ASA physical status 1 female patients undergoing lower abdominal surgery. The alfentanil requirements are considerably less when given as a supplement to propofol (4 μg/ml) compared to nitrous oxide (66%). Taking into account the anesthetic potencies of the concentrations of nitrous oxide and propofol that were studied, we conclude that alfentanil combined with propofol exerts a greater anesthetic effect compared to alfentanil combined with nitrous oxide. The speed of recovery after alfentanil/propofol anesthesia was rapid and comparable to that following alfentanil/nitrous oxide.

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** Sanford TJ, Smith NT, Weinger MB, Benthuysen JL, Head N: The effect of midazolam pretreatment on alfentanil-induced muscle rigidity (abstract). ANESTHESIOLOGY 69:A556, 1988, and Blasco TA, Smith NT, Sanford TJ, Benthuysen JC, Dec-Silver H, Head N: A clinical study of the effects of various pretreatment agents on alfentanil-induced rigidity: EMG data (abstract). ANESTHESIOLOGY 63:A380, 1986.

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