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Effects of Combining Propofol and Alfentanil on Ventilation, Analgesia, Sedation, and Emesis in Human Volunteers

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Background: Propofol and alfentanil frequently are administered together for intravenous sedation. This study investigated pharmacokinetic and pharmacodynamic interactions between propofol and alfentanil, at sedative concentrations, with specific regard to effects on ventilation, analgesia, sedation, and nausea.

Methods: Ten male volunteers underwent steady-state infusions on 3 separate days consisting of propofol alone, al-

fentanil alone, or a combination of the two. Target plasma concentrations for propofol were 150, 300, and 600 ng/ml for 1 h at each concentration; for alfentanil it was 40 ng/ml for 3 h. Assessment included serial measurements of (1) ventilatory function (minute ventilation, carbon dioxide production, end-tidal carbon dioxide, ventilatory response to rebreathing 7% CO₂); (2) analgesia (subjective pain report in response to graded finger shock and evoked potential amplitude); (3) sedation (subjective rating, observer scores, and digit symbol substitution test); (4) nausea (visual analog scale, 0-100 mm).

Results: During combination treatment, propofol plasma concentration was 22% greater than during propofol alone using replicate infusion schemes ($P < 0.009$). End-tidal carbon dioxide was unchanged by propofol, and increased equally by alfentanil and alfentanil/propofol combined (Δ end-tidal carbon dioxide 7.5 and 6.2 mmHg, respectively). Analgesia with propofol/alfentanil combined was greater than with alfentanil alone. (Pain report decreased 50% by PA vs. 28% for alfentanil, $P < 0.05$). Sedation was greater with propofol/alfentanil combined than with alfentanil or propofol alone (digit symbol substitution test 30 for propofol/alfentanil combined vs. 57 for alfentanil, and 46 for propofol, $P < 0.05$). Nausea occurred in 50% of subjects during alfentanil, but in none during propofol/alfentanil combination treatment.

Conclusions: The combination of propofol and alfentanil produced greater sedation and analgesia than that with either drug alone. Propofol offset the emetic effects of alfentanil. Equivalent depression of the carbon dioxide response curve, and elevation of end-tidal carbon dioxide occurred with propofol/alfentanil combined and alfentanil. (Key Words: Analgesia, opioids: alfentanil. Anesthetics, hypnotic: propofol. Pharmacokinetics: plasma concentration. Sedation: cognitive function. Ventilation: measurement.)

PROPOFOL (2,4-diisopropylphenol) is a sedative-hypnotic drug commonly employed for sedation because it permits rapid recovery of mental function with a relatively low incidence of unwanted side effects.¹⁻³ Alfentanil, an opioid with a similarly rapid recovery, frequently is combined with propofol when analgesia as well as sedation is desired. The efficacy and safety of simultaneously administering these two drugs for sedation has not been thoroughly evaluated. Unresolved issues include: (1) the ventilatory effects of combining

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the two drugs (2) how propofol affects opioid-induced analgesia and various opioid-related side effects and (3) how alfentanil affects the sedative properties of propofol.

Propofol alone, when administered by continuous infusion, typically permits adequate spontaneous ventilation.⁴ Clinically, it has been our observation that the administration of an opioid in combination with propofol often causes depression of ventilation that persists for several minutes with relatively little change in oxyhemoglobin saturation. We therefore postulated that the combination of propofol with an opioid (alfentanil) might decrease ventilation partly in response to a decrease in metabolic demands (oxygen consumption and carbon dioxide production) such that less ventilation would be required to maintain adequate gas exchange.

The effects of propofol on opioid-induced analgesia also are unknown. There is some evidence that propofol alone has mildly analgesic properties.⁵ In contrast, barbiturates, also frequently employed for sedation, may have antianalgesic properties.^{5,6}

A third area of interest is the effect of alfentanil on the potency of propofol as a sedative. Vinik *et al.* recently reported that propofol and alfentanil act synergistically in causing loss of consciousness when both drugs are administered as bolus doses for induction of anesthesia.⁷ However, the effects of alfentanil on level of consciousness during continuous propofol infusion have not been studied. Opioids appear to reduce requirements for inhalational anesthetics in a concentration-dependent, nonlinear fashion⁸; stepwise increments of plasma opioid concentrations have a gradually diminishing effect on reducing minimum alveolar concentration. Thus, the pharmacodynamic interaction between alfentanil and propofol demonstrated by Vinik *et al.* at relatively high concentrations of the two drugs may not predict their combined action at lower sedative concentrations.

Additionally, there is evidence of pharmacokinetic interactions between propofol and opioid drugs (*e.g.*, fentanyl) that could contribute to the effects of this drug combination.^{9,10} Whether such pharmacokinetic interactions occur with all opioids, and how such interactions might relate to pharmacodynamic interactions between the two drugs remains at issue.

We undertook this study to determine the pharmacokinetic and pharmacodynamic effects of combining alfentanil with propofol, with specific regard to effects on (1) ventilation; (2) analgesia; (3) level of con-

sciousness; and (4) subjective side effects including emetic symptoms, pruritus, and mood. The study was performed in normal human volunteers who, on separate occasions, received intravenous infusions of propofol, alfentanil, and a combination of the two to attain targeted steady-state plasma drug levels. Our results revealed both pharmacokinetic as well as pharmacodynamic interaction between propofol and alfentanil at plasma drug concentrations that are clinically employed to achieve sedation and analgesia.

Materials and Methods

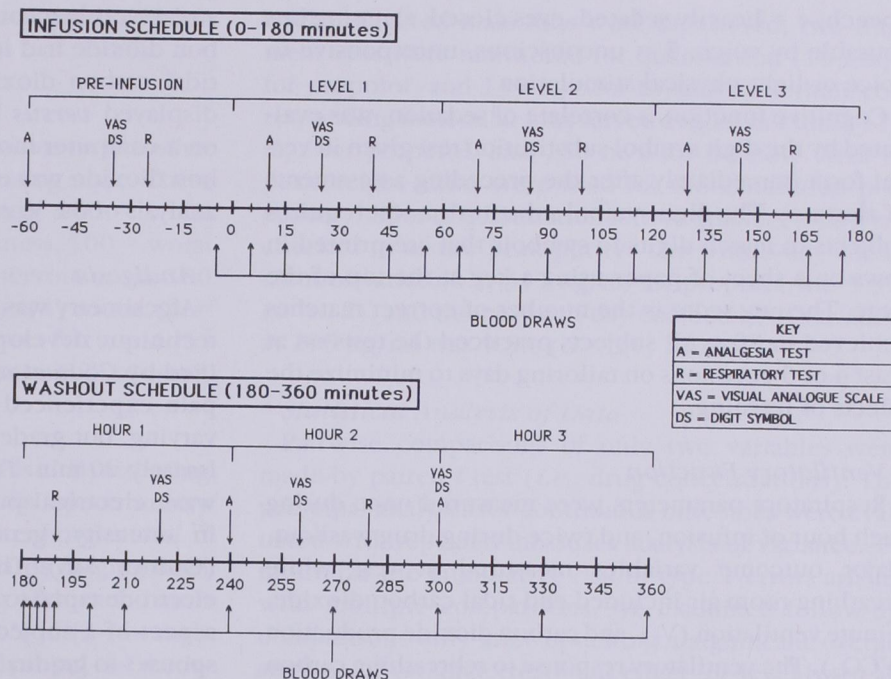
The institutional review board at the Fred Hutchinson Cancer Research Center approved this study for performance with paid human volunteers. A crossover design was used in which ten subjects received all three of the following treatments in a randomized, counter-balanced sequence: a 3-h infusion of propofol, alfentanil, or both propofol and alfentanil simultaneously. The pharmacokinetic parameters of propofol and alfentanil in each subject were predetermined on two separate days. Plasma drug concentration-time data from the preliminary sessions were fitted to either a two- or three-compartment model. Estimates of the pharmacokinetic parameters permitted design of a bolus-elimination-transfer-based infusion scheme¹¹ to achieve target steady-state plasma concentrations of drug on the three subsequent treatment days.

For the preliminary alfentanil session, each subject received a 15- μ g/kg intravenous bolus dose of alfentanil. Because of evidence of nonlinearity of low-dose pharmacokinetics of propofol in preliminary studies, propofol kinetics were best determined using a 1.5-h loading dose plus infusion regimen that would achieve a peak plasma concentration near the mid-target level of 300 ng/ml.

Propofol infusions were designed to maintain steady plasma concentrations at 150, 300, and 600 ng/ml for successive 1-h periods in an incremental fashion. Propofol was delivered by an IVAC 1500 pump (San Diego, CA) controlled by a bolus-elimination-transfer algorithm implemented on a Macintosh Plus computer (Apple, Cupertino, CA). Alfentanil infusions were intended to maintain a constant plasma drug concentration at 40 ng/ml for the entire 3 h of testing. Alfentanil was delivered by an Abbott/Shaw LifeCare pump (North Chicago, IL) controlled by a Toshiba T1100 Plus computer (Tokyo, Japan). Identical infusion schemes were used for propofol and alfentanil whether drugs were

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Fig. 1. Protocol design for each of treatment days. A = algesimetry, R = respiratory testing, VAS = visual analog scale; DS = digit symbol substitution test; OS = observer score. Vertical arrows signify times of blood sampling.



infused alone, or simultaneously. Both of these computer-controlled systems have been used extensively in our laboratory and have been described in detail elsewhere.¹¹⁻¹³

Subjects and Preparation

Ten men, aged 21-30 yr (mean 23.8 yr, SE 0.8) with at least 2 yr of college education, participated in this study. They were free of chronic medical illness, denied recent drug/alcohol abuse, and were taking no medications. All were within 20% of ideal body weight (weight 75.1 kg, SE 3.3; height 180 cm, SE 2.1). All subjects signed a written informed consent before participation in the study. Subjects fasted after midnight on the night before study until after collection of the last blood sample. On arrival, subjects received 7 ml/kg 5% dextrose in Lactated Ringer's solution intravenously over approximately 30 min, followed by a maintenance infusion of 1.5 ml/kg for the remainder of the study. Intravenous catheters were inserted in both arms, one for drug infusion, and one for blood sampling. All loading doses and infusions commenced at time 0, whether one or two drugs were being administered. Blood samples (6 ml) were obtained at baseline (before drug infusion) and at 5, 15, 30, 45, and 55 min during each hourly period. At termination of the infusions, blood was sampled at 1, 3, 5, 7, 10,

20, 30, 60, 90, 120, 150, and 180 min during drug washout. Blood samples were kept on ice and centrifuged at the end of the study to obtain plasma. A portion of the plasma underwent immediate processing for the assay of propofol. The remaining plasma was stored at -20°C for the analysis of alfentanil at a later time.

Level of consciousness, respiratory function, analgesia, and miscellaneous side effects (nausea, vomiting, pruritus, mood) were evaluated before and during each hour of infusion, and twice during drug washout to determine drug effects at each of the targeted concentrations when administered individually or in combination. Subjects, but not the investigators, were blinded as to which treatment they were receiving. Infusion tubing was wrapped to prevent visual recognition of propofol. Figure 1 illustrates the sequence of effect measurements and blood sampling.

Sedation

Both subject and observer ratings were used to quantify level of consciousness. Subjects rated alertness using a visual analog scale anchored by the descriptors "wide awake" (100) and "can't keep my eyes open" (0). Two trained observers rated consciousness using a continuous scale that ranged from 1 to 5, where 1 = wide awake; 2 = mildly sedated, relaxed; 3 = moderate sedation, spontaneously awakens but with slurred

speech; 4 = heavily sedated, eyes closed, sleeping but rousable by voice; 5 = unconscious, unresponsive to voice or light physical stimulation.

Cognitive function, a correlate of sedation, was evaluated by the digit symbol substitution test given in verbal form immediately after the preceding assessments of alertness. The digit symbol substitution test requires subjects to match digits to symbols that are printed in rows on a sheet of paper using a key at the top of the page. The raw score is the number of correct matches achieved in 90 s. All subjects practiced the tests on at least 4 or 5 occasions on tailoring days to minimize the effects of learning.

Ventilatory Function

Respiratory parameters were measured once during each hour of infusion, and twice during drug washout. Major outcome variables measured at rest while breathing room air included end-tidal carbon dioxide, minute ventilation (V_E), and carbon dioxide production (VCO_2). The ventilatory response to rebreathing carbon dioxide (slope of V_E /end-tidal carbon dioxide) was measured by a modified Read rebreathing technique.¹⁴

Subjects breathed through a rubber mouthpiece into a circuit containing a series of one-way valves. They inspired room air or 7% CO_2 in 40% O_2 (balance nitrogen) through a closed circuit with a reservoir balloon. They exhaled across a pneumotach (model 3183, Hans Rudolph, Kansas City, MO). Pressure and flow across the pneumotach were measured by a variable reluctance transducer (Validyne model MP 45-1-871) with a respiratory flow integrator (VF 156 = 871), using a carrier-demodulator to convert the signal to flow *versus* time. Gas flows were integrated to determine exhaled gas volume/breath, and cumulative exhaled gas volume/unit time. Carbon dioxide in exhaled gas was measured by an Andros OEM carbon dioxide analyzer (model 412, Andros, Inc., Berkeley, CA) and input to a computer.

When a stable ventilatory pattern had been established (*i.e.*, a relatively constant end-tidal carbon dioxide), end-tidal carbon dioxide was determined as the mean value of five exhaled breaths, while the subject breathed room air. Exhaled gas was then collected for 3 min in a 50-l neoprene collection bag, mixed exhaled carbon dioxide concentration was determined, and the VCO_2 was calculated as the product of the fractional carbon dioxide gas concentration and the exhaled gas volume (corrected to BTPS). The subjects rested for 2 min, and then breathed through a closed circuit with

a reservoir bag containing 7% CO_2 , until end-tidal carbon dioxide had increased by at least 20 mmHg. End-tidal carbon dioxide concentration was plotted and displayed *versus* breath-to-breath minute ventilation on a computer monitor. The slope of V_E /end-tidal carbon dioxide was estimated by least-squares regression analysis of the V_E *versus* end-tidal carbon dioxide data.

Analgesia

Algesimetry was performed using a modification of a technique developed by Chapman *et al.*^{15,16} and modified by Coda *et al.*^{17,18} Subjects evaluated severity of pain experienced during a series of finger shocks of varying, but graded intensity over a period of approximately 20 min. The pain stimulus consisted of square wave electrical pulses of 5 ms duration, 0.5–2.0 mA in intensity, generated by a Grass S44 stimulator (Quincy, MA). The shocks were applied *via* a silver electrode taped to an abraded area of skin on the ventral aspect of a subject's finger. Subjects defined pain responses to gradually increasing levels of current in the baseline period. Subjects rated their pain intensity on a continuous numeric scale of 0–5 using the lever of a slide potentiometer, where 0 = slight sensation; 1 = just perceptible pain; 5 = strong pain without wincing or withdrawing. Once the baseline stimulus-response relationship was established, shocks were delivered at intensity levels 3 and 5, with an interstimulus interval of 6–8 s in 3 sets of 30 shocks with a 2-min rest between sets; the order of intensity and intershock interval were varied at random. Stimulus intensities corresponding to pain ratings of 3 and 5 were established anew on each testing day. During testing sessions, the scale was expanded from 0–5 to 0–6 to accommodate potential increases in perceived pain beyond the maximum of 5 as originally defined in the baseline period. Subjective pain responses to level 3 and level 5 shocks at each steady-state plasma drug level were averaged independently to derive a subjective pain score for each level of electrical stimulation. Only the data obtained at the level 5 shocks are presented herein.

Simultaneously, evoked potential responses to the cutaneous shocks (peak-to-peak amplitude for N150-P250) were recorded *via* a scalp electrode placed at the vertex of the skull with a reference to linked ears. A forehead electrode served as a ground. Simultaneous monitoring of eye blink artifacts permitted rejection of contaminated records and repetition of rejected trials. The summated average of 30 consecutive shocks constituted a record with peak to peak amplitude scored

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in μV . Three sets of 30 records were averaged to obtain a mean score for 90 stimuli.

Subjective Side Effects

Subjects provided subjective evaluations on five other side effects using a 100-mm visual analog scale. These included: (1) nausea (0 = no nausea, 100 = worst possible); (2) itchiness (0 = no itchiness, 100 = worst possible); (3) nervousness (0 = not nervous at all, 100 = as nervous as I could possibly be); (4) mood (0 = worst I've ever felt, 100 = best I've ever felt), and (5) dizziness (0 = no dizziness, 100 = constant dizziness).

Drug Analysis

Plasma concentration of alfentanil was analyzed using a modified gas chromatography-mass spectrometry method originally described by Woestenborghs *et al.*¹⁹ and Weldon *et al.*²⁰ Calibration standards ranging from 2 to 200 ng/ml were prepared along with each batch of samples. The internal standard was N-{1-[3-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)propyl-4-(methoxymethyl)-4-piperidinyl]-N-phenyl propanamide hydrochloride (R38527). The within-day coefficient of variation for the alfentanil assay at a concentration of 20 ng/ml was 3.5%. The between-day coefficient of variation at 20 ng/ml of alfentanil was 9.9%. The detection limit for alfentanil was 1 ng/ml.

Plasma concentration of propofol was analyzed by a gas chromatography-mass spectrometry method developed in our laboratory. A 0.5-ml plasma sample was combined with 1 ml of 1 M pH 4 phosphate buffer, 500 ng of the internal standard (thymol), and 200 μl heptane/isoamyl alcohol (97/3, vol/vol) in a 13 \times 100 mm glass screw-top tube and shaken for 15 min. After centrifugation, an aliquot of the organic phase was transferred to an autosampler vial.

The gas chromatographic-mass spectrometric analysis of propofol was performed on a Hewlett-Packard 5989 GC-MS machine operated in the electron impact mode (70 eV). Chromatographic resolution was achieved on a 20 m \times 0.25 mm, 1 μm thickness film J & W DB1 column (Folsom, CA). The oven temperature was initially held at 150°C for 0.75 min, then ramped to 170°C at 10°C per minute and returned to 250°C at 40°C per minute. The injector temperature was set at 250°C and pressure programmed to maintain constant flow starting at 25 psi. A 2- μl aliquot of the sample extract was injected in the splitless mode. Mass spectrometer source, quadrupole, and transfer line temperatures were 250°C, 100°C, and 250°C, respec-

tively. Selected mass ions were monitored; two fragment ions were monitored for quantitation (163 m/z for propofol, and 135 m/z for thymol) and their corresponding molecular ions served as qualifier ions (178 m/z for propofol, and 150 m/z for thymol). Area or peak height ratios were used for the calibration procedure. Ratios of quantitation ions to qualifier ions were checked to assure peak purity. The within-day coefficient of variation at 317 ng/ml for propofol was 5.9% (n = 12), and the between-day coefficient of variation at 295 ng/ml was 9.5% (n = 29; 25 days).

Statistical Analysis of Data

Pairwise comparisons of only two variables were made by paired *t* test (*i.e.*, drug concentrations). The principal analyses for continuous outcomes were evaluated with repeated-measures analysis of variance. To minimize the cumulative risk of type 1 errors arising with multiple comparisons, we examined follow-up comparisons only after obtaining a significant overall analysis of variance treatment effect, or level-by-treatment interaction. *Post hoc* comparisons of individual time points within, or between treatments were made using Fisher's least possible difference testing.²¹

Although continuous by design, the nausea, itchiness, alertness, and sedation outcomes displayed nonnormal distributions and heterogeneous variances. Conventional parametric and rank-order methods are not generally valid for such distributions. For tests involving these variables, we constructed bootstrapped 95% confidence intervals for the relevant contrasts based on 10,000 replicates for each test. These confidence intervals are asymptotically valid approximations of the exact, but unknown, confidence intervals. The standard errors provided in the Tables and Figures for these variables are merely descriptive because they are based on normal distribution theory.

Results

Plasma Drug Concentrations

The time course of propofol and alfentanil concentrations for the ten subjects are shown in figures 2 and 3, respectively. Mean propofol concentrations (table 1) (146, 292, and 633 ng/ml) during infusion of propofol alone were within 1.8–5.5% of target (150, 300, and 600 ng/ml, respectively). Using the terminology of Varvel *et al.*,²² the average median absolute performance error (median deviation from the target expressed as a percent

of the target concentration) was 18.5%. The average median prediction error (bias) was -1.017% , where average median prediction error = average median difference from the predicted values calculated as a signed value. During simultaneous infusion of propofol and alfentanil, mean propofol concentrations were 21–22% higher than during infusion of propofol alone (184, 356, and 771 ng/ml $P < 0.011$). During infusion of alfentanil alone (A), mean alfentanil concentrations (41.3, 42.4, and 40.6 ng/ml at periods 1, 2, and 3) were within 1.4–6.0% of the target of 40 ng/ml. The average median absolute performance error was 16.7%, and average median prediction error was $+5.57\%$. When combined with propofol infusion, alfentanil concentrations exceeded those observed with alfentanil alone (46.3, and 46.9 ng/ml at periods 2 and 3 respectively, $P < 0.0247$ and < 0.0008).

Sedation

Table 2 demonstrates loss of alertness or increasing sedation that occurred with increasing levels of propofol during both *propofol* and propofol/alfentanil treatments as assessed by subjective report or observer score. The effects are plotted *versus* drug concentration in figure 4. Subjectively, the addition of alfentanil increased sedation (decreased alertness) afforded by propofol ($P < 0.05$ for propofol/alfentanil *vs.* propofol). Enhanced effects were also demonstrated in the digit symbol substitution test, an objective assessment of cognitive function ($P < 0.05$ for propofol/alfentanil *vs.* propofol). Maximal sedation (mean observer score 4.03, SE 0.17), attained at level 3 on the combined treatment day corresponded to a condition in which subjects were sleeping but rousable by voice or light physical stimulation.

Ventilation

A summary of all of the ventilatory parameters is presented in table 3; in figure 5, the respiratory effects are plotted *versus* mean drug concentration. When the two drugs were coadministered, depression of resting minute ventilation was more severe than that which occurred with alfentanil alone, but the associated rise in end-tidal carbon dioxide was equivalent. The latter is explained by the finding that although ventilation was more depressed by the propofol/alfentanil treatment, VCO_2 was reduced to a proportionate degree. Similarly, depression of the ventilatory response to rebreathing carbon dioxide was no greater during level 3 of the combined treatment than was observed with alfentanil alone.

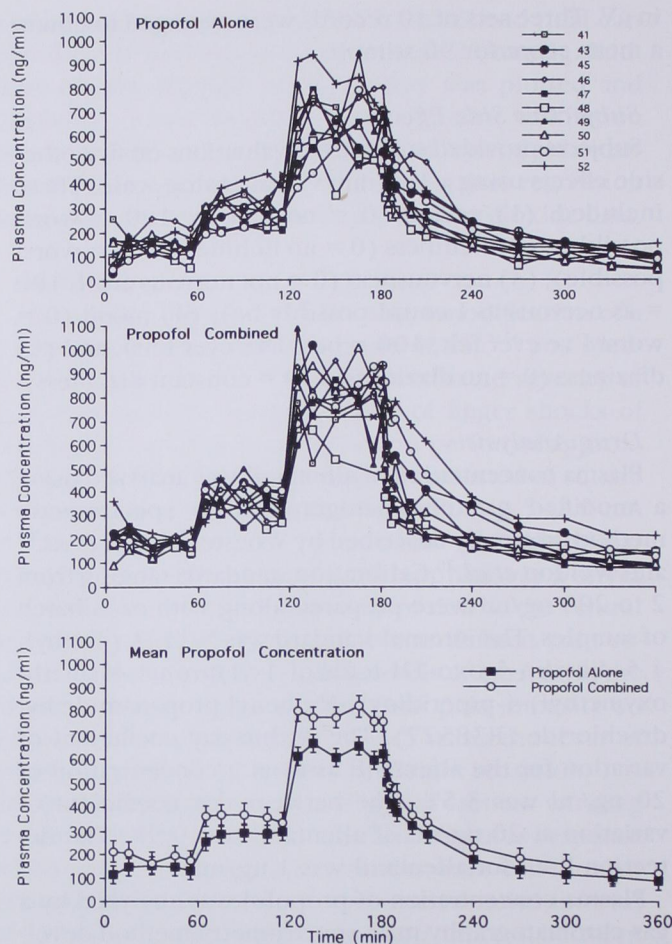


Fig. 2. Individual (upper two panels) and mean (lower panel) plasma propofol concentrations (ng/ml) (\pm SE) during infusion (0–180 min), and during drug washout (180–360 min). See table 1 for statistical comparisons. Closed squares = treatment with propofol; open circles = treatment with alfentanil and propofol.

Propofol alone had no significant effect on end-tidal carbon dioxide, ventilation, or VCO_2 , but caused a small decline in slope of the carbon dioxide response curve (22% at level 3). As expected, alfentanil alone caused significant depression of minute ventilation (22–25% at levels 1–3, $P < 0.05$), which was proportionately somewhat greater than depression of VCO_2 (12–19%). This accounts for a significant rise in end-tidal carbon dioxide (15–19%, $P < 0.05$, compared to baseline). Alfentanil alone caused 33–41% depression of the ventilatory response to rebreathing carbon dioxide.

Analgesia

Alfentanil alone caused a 28% reduction in subjective pain report ($P < 0.05$; (fig. 6 and table 4). Evoked

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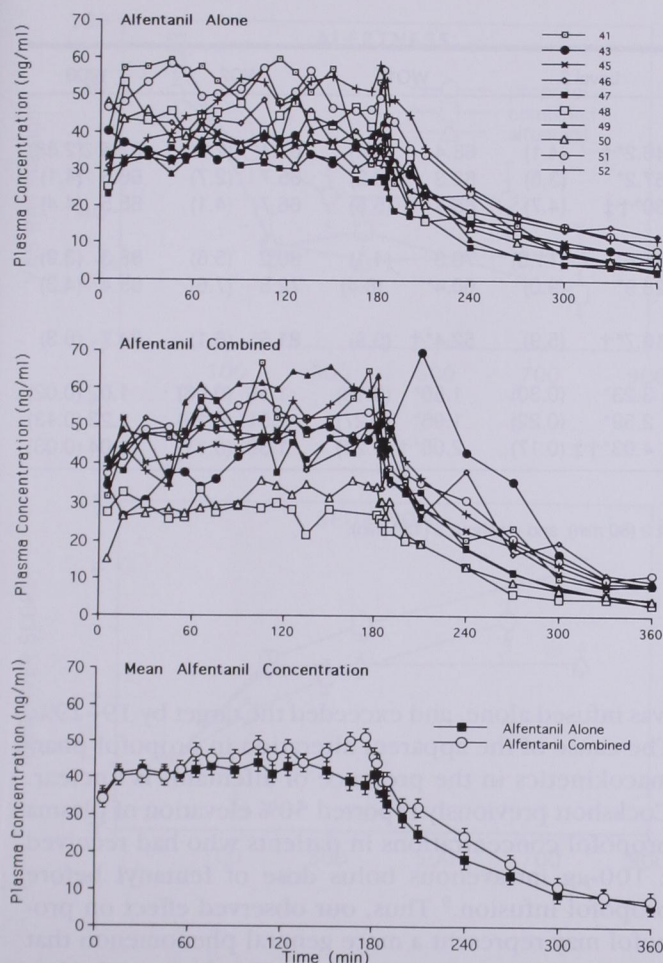


Fig. 3. Individual (upper two panels) and mean (lower panel) plasma alfentanil concentrations (ng/ml; \pm SE) during infusion (0–180 min), and drug washout (180–360 min). See table 1 for statistical comparisons. Closed squares = treatment with alfentanil; open circles = treatment with alfentanil and propofol combined.

potentials amplitude was diminished more numerically than the subjective pain report during alfentanil infusion (60% at level 3, $P < 0.05$). Propofol significantly

enhanced alfentanil-induced analgesia at level 3 based on subjective pain report as compared to the effects of alfentanil alone (50% vs. 28% reduction in pain report; 2.4 vs. 3.4, $P < 0.05$ for propofol/alfentanil vs. alfentanil). Propofol alone produced a modest (21%), but statistically significant reduction in subjective pain score at the highest concentration of 633 ng/ml ($P < 0.05$). Evoked potential amplitude diminished significantly at the lower plasma concentrations of propofol; *i.e.*, before any detectable change occurred in subjective pain report (43%, 66%, and 75% at levels 1, 2, and 3, respectively; table 4). Combining propofol with alfentanil yielded analgesia and sedation superior to that attained with either drug alone, and with no greater change in end-tidal carbon dioxide than that observed with alfentanil alone (figs. 4–6).

Miscellaneous Symptoms

Five of the ten subjects experienced nausea during treatment with alfentanil alone (fig. 7). Three of these subjects vomited repeatedly during, and for at least 1 h after termination of the alfentanil infusion. Propofol alone produced no emetic symptoms. With the combined treatment, mild nausea occurred transiently in one subject during drug washout; none of the subjects vomited at any time. Nausea experienced with alfentanil was significantly greater than with propofol, or propofol/alfentanil treatments (using bootstrapped confidence intervals). Pruritus occurred in the majority of subjects during alfentanil infusion (fig. 8); a similar pattern of response emerged during the propofol/alfentanil treatment. Differences were significant between propofol and the alfentanil or propofol/alfentanil treatments.

There were no statistically significant effects of drug treatments reported by subjects on mood, nervousness, or dizziness. Dizziness, however, was reported occasionally by individual subjects.

Table 1. Plasma Drug Concentrations

Treatment	Propofol (ng/ml)			Alfentanil (ng/ml)		
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
Propofol (P)	144* (10.8)	292* (19.8)	633* (32.4)	—	—	—
Alfentanil (A)	—	—	—	40.0 (21.5)	42.4† (2.3)	41.0† (2.2)
Propofol/alfentanil (PA)	183.7* (7.3)	356.8* (13.2)	771.2* (30.2)	39.3 (2.4)	46.5† (3.2)	47.2† (3.5)

Values are mean (SE).

* $P = 0.0097$, 0.0021 , and 0.0036 for PA versus P at levels 1, 2, and 3, respectively.

† $P = 0.0247$ and 0.0008 for PA versus A at levels 2 and 3, respectively.

Table 2. Measures of Alertness, Sedation, and Cognitive Function

Test	Baseline	Level 1	Level 2	Level 3	WO1	WO2	WO3
DSST							
Propofol (P)	65.8 (4.5)	59.9 (3.96)	55.5* (4.56)	46.2*† (4.1)	66.4 (4.4)	67.4 (2.98)	67.5 (2.88)
Alfentanil (A)	68.9 (5.6)	58.4* (3.1)	55.1* (2.5)	57.2* (3.6)	62.3 (3.2)	65.7 (2.7)	66.6 (4.1)
Combined (PA)	70.3 (4.7)	57.7* (5.1)	49.4* (4.6)	30*†‡ (4.7)	65.1 (5.5)	66.7 (4.1)	65.5 (4.4)
Alertness							
Propofol (P)	77.1 (6.3)	59.3 (9.6)	46.1* (9.5)	45.5* (11.6)	76.3 (4.1)	80.2 (5.8)	88.3 (3.9)
Alfentanil (A)	88.4 (6.6)	31.9* (8.1)	26.4* (7.7)	28.9* (9.0)	60.4* (8.4)	72.8 (7.6)	85.4 (4.3)
		30.4*† (9.6)	35.4* (10.1)				
Combined (PA)	93.2 (3.97)			16.7*† (5.9)	52.4*† (9.9)	81.5* (6.1)	84.7 (6.3)
Observer score							
Propofol (P)	1.0 (0)	1.79* (0.19)	2.34* (0.27)	3.23* (0.30)	1.50* (0.10)	1.16 (0.06)	1.02 (0.02)
Alfentanil (A)	1.0 (0)	2.52* (0.19)	2.53* (0.19)	2.59* (0.22)	1.96* (0.27)	1.51* (0.16)	1.23 (0.13)
Combined (PA)	1.0 (0)	2.62*† (0.13)	3.13*†‡ (0.22)	4.03*†‡ (0.17)	2.08*† (0.24)	1.39 (0.11)	1.04 (0.03)

Values are mean (SE).

DSST = digit symbol substitution test; WO1, 2, and 3 = washout 1 (40 min), washout 2 (80 min), and washout 3 (120 min).

* $P < 0.05$ versus baseline.

† $P < 0.05$, P versus PA.

‡ $P < 0.05$, A versus PA.

Discussion

The goals of this study were to determine the pharmacokinetic and pharmacodynamic effects of combining propofol and alfentanil as a means of providing sedation and analgesia of short duration.

Plasma Drug Concentrations

The target plasma drug concentration chosen for alfentanil (40 ng/ml) was deliberately modest and had previously been shown to cause a 30% reduction in subjective pain report while permitting adequate spontaneous ventilation.¹² The propofol targets were based on preliminary investigations in human subjects. Plasma concentrations in excess of 800 ng/ml, particularly when combined with alfentanil, were associated with excessive sedation and a tendency toward upper airway obstruction. At these deeper levels of sedation, subjects could not reliably evaluate pain stimuli, nor could they complete tests of mental function. Accordingly, the highest target level for propofol alone was set at 600 ng/ml.

The mean plasma drug concentrations of propofol during propofol infusion alone were within 5.5% of the predicted target. The median absolute performance error was 19%, and the median prediction error was minimal (-1.017%). When the two drugs were administered simultaneously, propofol concentrations in plasma were consistently greater than when propofol

was infused alone, and exceeded the target by 19–29%. The cause of the apparent alteration in propofol pharmacokinetics in the presence of alfentanil is unclear. Cockshott previously reported 50% elevation of plasma propofol concentrations in patients who had received a 100- μ g intravenous bolus dose of fentanyl before propofol infusion.⁹ Thus, our observed effect on propofol may represent a more general phenomenon that occurs with a variety of opiates. The finding of alfentanil-induced elevation of plasma propofol concentration could be related to altered propofol distribution, and/or metabolic clearance.

Of considerable interest is the recent report by Matot *et al.*¹⁰ of a significant first-pass uptake of propofol in cat lungs (60%). Uptake of propofol by the lung was reduced by pretreatment with fentanyl to 40%. This may explain Cockshott's observations of a higher plasma propofol concentration in humans when propofol infusion was preceded by a bolus of fentanyl. Uptake of alfentanil by the lungs has also been demonstrated in man (first-pass extraction of 36–80%) by Taeger *et al.*²³ Although a portion of the initially extracted alfentanil immediately dissociated ($t_{1/2}$ 0.28 min) and was redistributed to other tissues, a large portion of drug (15–50%) remained bound in the lung for a longer period of time. Binding is believed to be caused by hydrophobic interaction. Thus, alfentanil may compete with propofol in first-pass pulmonary uptake allowing a greater quantity of pro-

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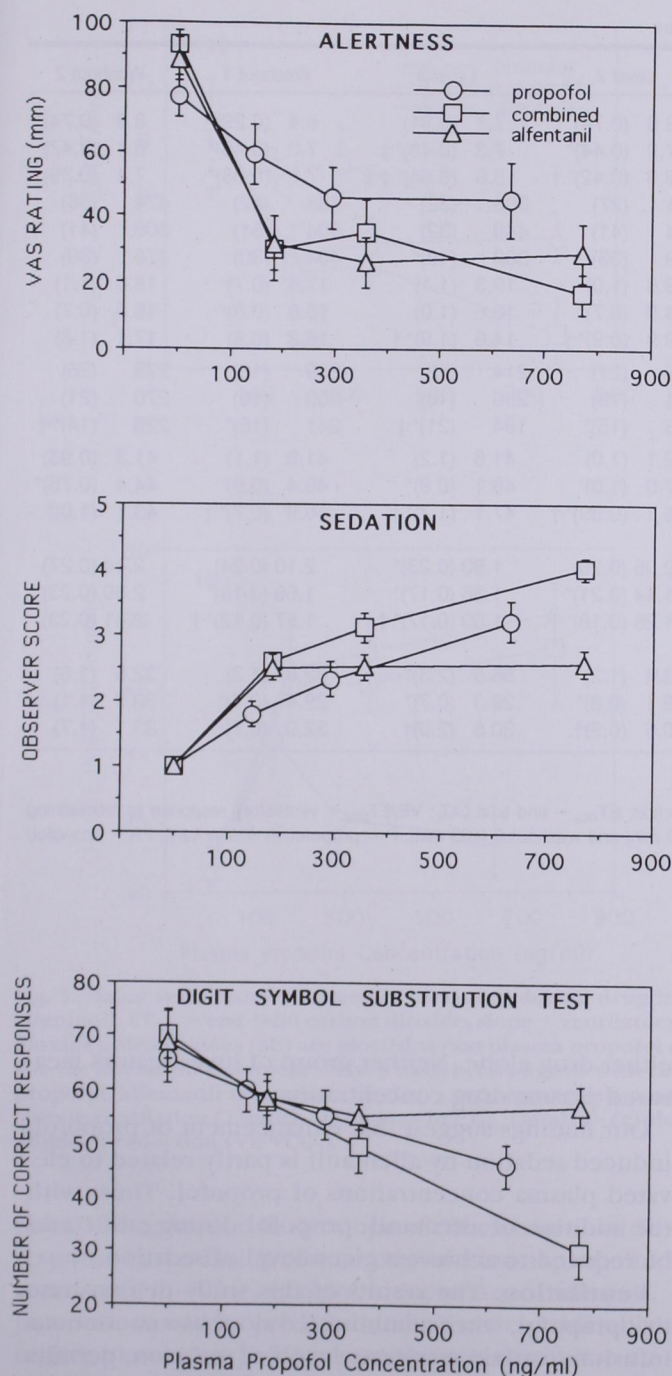


Fig. 4. Assessment of alertness by subjects using a visual analog scale (top), sedation by an observer (middle), and performance on digit symbol substitution test (bottom). Mean values (SE) are plotted versus plasma propofol concentrations for propofol and propofol/alfentanil treatments. For the alfentanil treatment, values have been aligned with the results of measurements made at comparable times during the propofol/alfentanil treatment. Circles = treatment with propofol; squares = treatment with alfentanil/propofol; triangles = treatment with alfentanil.

propofol to reach the systemic circulation than would otherwise occur.

Other explanations obviously exist such as a reduction in cardiac output, or hepatic clearance of propofol by alfentanil. Because neither cardiac output or hepatic clearance were measured, we can only speculate on the causal mechanisms of the observed interaction. Regardless, the clinical relevance of our observation is that standard dosing rates of propofol, when administered with alfentanil, may yield higher than predicted concentrations of propofol in plasma.

There was also a tendency to greater alfentanil concentrations during combined propofol/alfentanil *versus* alfentanil that was significant at the higher concentrations of propofol (level 2 and 3, $P < 0.0008-0.0247$). This is consistent with a report by Gepts *et al.* that plasma alfentanil concentrations designed to achieve a target of 300 ng/ml were approximately 20% higher than predicted when infused simultaneously with an infusion of propofol. There are several reasons to suspect that propofol might alter the kinetics of alfentanil. Propofol has been reported to inhibit the oxidative metabolism of alfentanil by microsomal cytochrome P450 enzymes *in vitro*.^{25,26} As described previously, decreased uptake of alfentanil in the lungs due to competitive binding of propofol might also promote elevated plasma concentrations of alfentanil. The current study may be criticized for the use of venous rather than arterial drug concentrations because arterial blood concentrations may more closely approximate those that exist at the "effect site." However, it is likely that arteriovenous differences between arterial and venous blood of the forearm were minimal with prolonged infusions.

Drug Effects

Sedation. As expected, both propofol and alfentanil depressed level of consciousness. With propofol, the changes appear to be related to concentration. The combination of the two drugs produced sedation that was greater than that observed with either drug alone (figure 4). Obviously, reliance on subjective evaluation may not provide accurate assessment while subjects are under the influence of medication. We therefore used the digit symbol substitution test as objective evidence of subjects' level of mental function. The observer score was used primarily to relate the depth of sedation to criteria that are clinically relevant. Because the latter were not performed by blinded observers they are subject to "observer

Table 3. Ventilatory Parameters during Drug Infusion and Washout

Variable	Treatment	Baseline	Level 1	Level 2	Level 3	Washout 1	Washout 2
VE (L/min)	P	8.3 (0.35)	8.5 (0.4)	8.6 (0.74)	7.7 (0.81)	8.4 (0.29)	8.8 (0.74)*
	A	9.3 (0.51)	7.0 (0.53)*	7.2 (0.44)*	7.3 (0.43)*‡	7.3 (0.46)*	8.1 (0.47)
	PA	9.6 (0.44)	6.7 (0.6)*†	6.8 (0.42)*†	5.6 (0.64)*†‡	7.6 (0.38)*	7.4 (0.39)†
VT (ml)	P	464 (40)	466 (34)	461 (27)	395 (32)	483 (22)	474 (36)
	A	510 (32)	429 (43)	484 (41)	440 (32)	504 (51)	506 (41)
	PA	536 (25)	446 (30)*†	469 (33)	382 (49)*	484 (30)	475 (39)
f (resp/min)	P	18.4 (1.0)	19.0 (1.3)	18.6 (1.0)	19.3 (1.1)	17.5 (0.7)	18.8 (1.1)
	A	18.5 (1.0)	16.8 (0.9)	14.9 (0.7)*	16.6 (1.0)	15.6 (0.8)*	16.6 (0.7)
	PA	17.9 (0.9)	15.4 (1.0)*†	19.9 (0.9)*†	14.6 (1.9)*†	16.3 (0.8)	17.1 (1.3)
V _{CO₂} (ml/min)	P	251 (14)	260 (17)	259 (21)	214 (23)	259 (13)	273 (26)
	A	284 (17)	231 (19)*	251 (19)	250 (18)	250 (16)	270 (21)
	PA	289 (10)	215 (17)*	225 (15)*	184 (21)*†	241 (16)*	228 (14)*†
ET _{CO₂} (mmHg)	P	40.8 (0.91)	44.4 (1.0)	42.1 (1.0)	41.6 (1.2)	41.8 (1.1)	41.3 (0.93)
	A	40.6 (0.71)	46.5 (1.3)*	47.0 (1.0)*	48.1 (0.9)*	46.4 (0.9)*	44.4 (0.76)*
	PA	40.9 (0.67)	46.0 (1.1)*†	46.1 (0.89)*†	47.1 (1.7)*†	46.9 (0.7)*†	43.1 (1.0)*
VE/ET _{CO₂} (L · min ⁻¹ · mmHg ⁻¹)	P	2.3 (0.32)	2.24 (0.30)	2.06 (0.26)	1.80 (0.23)*	2.10 (0.24)	2.44 (0.27)
	A	2.31 (0.27)	1.54 (0.24)*	1.44 (0.21)*	1.36 (0.17)*	1.66 (0.19)*	2.39 (0.23)
	PA	2.49 (0.22)	1.17 (0.17)*†‡	1.26 (0.18)*†	1.00 (0.17)*†	1.57 (0.12)*†	2.41 (0.23)
VE/V _{CO₂} (L · min ⁻¹ · ml ⁻¹ · min ⁻¹)	P	33.4 (1.5)	33.4 (1.6)	33.4 (1.2)	36.5 (2.3)*	32.8 (1.3)	32.8 (1.6)
	A	32.9 (0.9)	30.6 (1.0)	29.1 (0.8)*	29.3 (0.7)*	29.4 (0.7)*	30.9 (1.1)
	PA	33.1 (1.1)	30.8 (1.1)	30.6 (0.9)†	30.6 (2.0)†	32.0 (0.7)	33.1 (1.7)

Values are mean (SE).

VE = minute ventilation; VT = tidal volume; f = respiratory rate; V_{CO₂} = CO₂ production; ET_{CO₂} = end-tidal CO₂; VE/ET_{CO₂} = ventilatory response to rebreathing CO₂; VE/V_{CO₂} = ventilation related to CO₂ production; WO1 and 2 = washout 1 (10 min) and washout 2 (100 min); P = propofol; A = alfentanil; PA = propofol/alfentanil.

* $P < 0.05$ versus baseline.

† $P < 0.05$, P versus PA.

‡ $P < 0.05$, PA versus A.

bias." However, evaluations were performed according to a set of objective criteria in an attempt to standardize the method of scoring.

It was not possible to determine from our data whether the sedative effects of the combined drugs were additive or synergistic. At best, one can say that the drugs appear to be mutually enhancing. This is consistent with reports by Vinik *et al.*⁷ and by Short *et al.*²⁷ that the combination of propofol and alfentanil is mildly synergistic in causing loss of consciousness. Using the fixed end point of "loss of consciousness," Vinik determined that the effective dose in 50% of subjects for a combination of propofol and alfentanil was 1.3 times the predicted value based on dose-response studies with either drug alone. Similarly, Short reported a 20% reduction in expected effective dose in 50% of subjects for hypnosis with alfentanil-propofol combinations over that predicted based on observations with

either drug alone. Neither group of investigators measured plasma drug concentrations.

Our findings suggest that enhancement of propofol-induced sedation by alfentanil is partly related to elevated plasma concentrations of propofol. Thus, with the addition of alfentanil, propofol dosing rate could be reduced to achieve a given level of sedation.

Ventilation. The results of this study demonstrate that propofol, when administered alone as a continuous infusion to attain moderate levels of sedation, permits adequate spontaneous ventilation. Even at the highest plasma levels of propofol (600–800 ng/ml), end-tidal carbon dioxide was not significantly elevated during infusion of propofol alone, and there was only mild depression of the ventilatory response to inhalation of 7% CO₂ (22%). There was also no evidence of desaturation (<95% saturation) by pulse oximetry. Goodman *et al.*⁴ reported adequate spontaneous ventilation,

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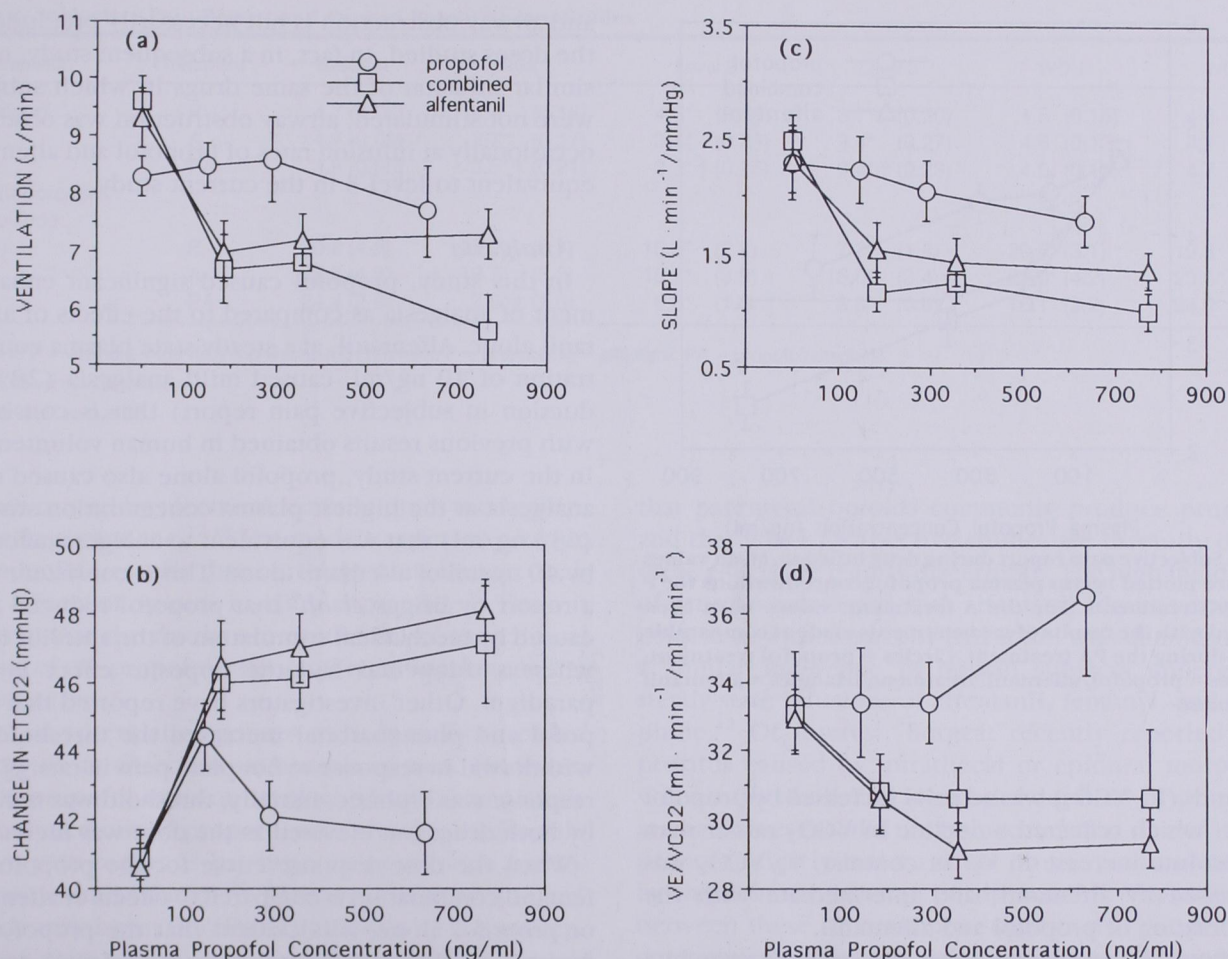


Fig. 5. Major ventilatory parameters measured during drug infusion for treatments with alfentanil, propofol, and propofol/alfentanil. ET_{CO_2} = end-tidal carbon dioxide; slope = ventilatory response to rebreathing 7% CO_2 (l/min/mmHg end-tidal carbon dioxide). Mean values (SE) are plotted versus plasma propofol concentrations for propofol and propofol/alfentanil treatments. For the alfentanil treatment, values have been aligned with the results of measurements made at comparable times during the propofol/alfentanil treatment. Circles = treatment with propofol; squares = propofol/alfentanil; triangles = alfentanil. (a) Minute ventilation (l/min); (b) change in ET_{CO_2} (mmHg); (c) slope of the carbon dioxide response curve; (d) ventilation/carbon dioxide production (VE/VCO_2).

but a 50% reduction in the slope of the carbon dioxide response curve during continuous infusion of propofol at rates of 100–200 $\mu\text{g/kg/min}$. Such rates of infusion, however, would be predicted to achieve considerably higher plasma propofol concentrations than were attained in the current study. In our subjects, the average rate of infusion required to maintain a constant plasma level of propofol at 633 ng/ml (*i.e.*, level 3) was approximately 43 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Similarly, Gepts reported that constant infusions of 50 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ caused deep sedation in 85%, and unconsciousness in 15% of patients undergoing surgery under regional anesthesia.²⁸

In this study, infusion of alfentanil alone caused significant depression of the carbon dioxide response curve, and modest carbon dioxide retention due to a decline in minute ventilation that exceeded simultaneous reduction in VCO_2 , consistent with the results of previous studies.¹²

Most importantly, although the addition of propofol to alfentanil caused greater depression of the carbon dioxide response curve and a greater decline in minute ventilation than was seen with alfentanil alone, the depression of minute ventilation was offset by a similar decline in VCO_2 that prevented any further rise in end-tidal carbon dioxide. Ventilation relative to metabolic

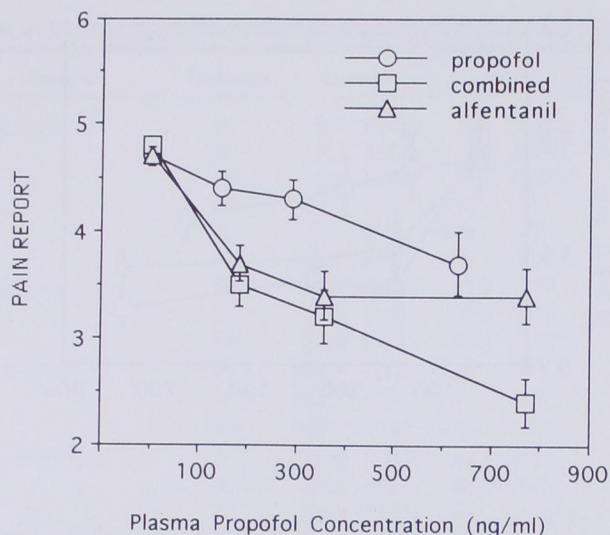


Fig. 6. Subjective pain report during drug infusion. Mean values (SE) are plotted versus plasma propofol concentrations for P and PA treatments. For the A treatment, values have been aligned with the results of measurements made at comparable times during the PA treatment. Circles = propofol treatment; squares = propofol/alfentanil treatment; triangles = alfentanil treatment.

demands (V_E/VCO_2) was actually increased by propofol alone, which reflected a decline in VCO_2 rather than an absolute increase in V_E . In contrast, V_E/VCO_2 was depressed by alfentanil, and intermediate with the combination of propofol and alfentanil.

It should be emphasized that our subjects were in a semirecumbent position and, although resting quietly in a soundproof chamber, they were stimulated frequently as part of the experimental protocol. They had a mouthpiece in place during the tests of ventilatory function. The level of activity may have prevented upper airway obstruction, and/or apnea and hypoxia that often occur in heavily sedated patients. Thus, the adequacy of ventilation with the treatments administered may be dependent on maintaining an adequate airway,

and airway obstruction is not necessarily precluded at the doses studied. In fact, in a subsequent study, using similar infusion of the same drugs in which subjects were not stimulated, airway obstruction was observed occasionally at infusion rates of propofol and alfentanil equivalent to level 3 in the current study.

Analgesia

In this study, propofol caused significant enhancement of analgesia as compared to the effects of alfentanil alone. Alfentanil, at a steady-state plasma concentration of 40 ng/ml, caused mild analgesia (28% reduction in subjective pain report) that is consistent with previous results obtained in human volunteers.¹² In the current study, propofol alone also caused mild analgesia at the highest plasma concentration studied (633 ng/ml) that was equivalent to analgesia afforded by 40 ng/ml of alfentanil alone. This is consistent with a report by Briggs *et al.*⁵ that propofol reduced pain caused by mechanical stimulation of the anterior tibia, whereas thiopental had the opposite effect in this paradigm. Other investigators have reported that propofol and phenobarbital increased the threshold for withdrawal in response to hot plate pain in rats.^{§§} The response was biphasic; initially, threshold was reduced by both drugs but elevated as the dose was increased.

When the dose-response curve for the propofol/alfentanil combination is compared to effects of alfentanil or propofol alone, it is evident that the propofol/alfentanil combination affords greater analgesia and sedation, but at no greater cost in terms of elevating end-tidal carbon dioxide (figs. 4–6). Whether enhancement of analgesia with propofol indicates specific pharmacologic action on nociceptive neurotransmission,^{|||}## or is simply a nonspecific side effect of sedation requires further clarification. However, because the response is opposite to that described with barbiturates in humans, it lends some credence to the hypothesis that propofol exerts specific effects on pain pathways other than that simply attributable to sedation alone. Coda *et al.* have also reported that the combination of a benzodiazepine (alprazolam) with morphine produced greater sedation, but did not enhance analgesia compared to morphine alone, suggesting again that sedation does not necessarily enhance analgesia.²⁹

As with all laboratory models of pain, one may question whether analgesia identified in this study predicts effects on pain in the clinical situation. Our laboratory has had considerable success in demonstrating concentration-related analgesia with opioids in response

§§ Wilder-Smith OHG, Kolletzki K, Naji P, Wilder-Smith CH: Propofol and thiopentone exhibit dose-dependent effects on heat pain thresholds in subanaesthetic doses (abstract). *Acta Anaesthesiol Scand* 1991; 35(suppl 96):47.

||| Jewett BA, Tarasiuk A, Gibbs L, Kendig JJ: Propofol and barbiturates: Depression of nociceptive neurotransmission in spinal cord (abstract). *ANESTHESIOLOGY* 1991; 75:A589.

Yamamura T, Ohtsuka H, Furumido IH, Tsutshara S, Kemmotsu G: Does propofol enhance the GABA-mediated synaptic transmission (abstract)? *ANESTHESIOLOGY* 1991; 75:A588.

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Table 4. Subjective Pain Report and Evoked Potential Amplitudes

Parameter	Treatment	Baseline	Level 1	Level 2	Level 3	WO 1	WO 2
Pain report	P	4.7 (0.08)	4.4 (0.16)	4.3* (0.18)	3.7* (0.30)	4.5 (0.15)	4.6 (0.12)
	A	4.7 (0.09)	3.7* (0.17)	3.4* (0.23)	3.4* (0.27)	4.6 (0.12)	4.7 (0.15)
	PA	4.8 (0.06)	3.5*† (0.21)	3.2*† (0.26)	2.4*† (0.23)	4.5 (0.12)	4.7 (0.07)
Evoked potential amplitude (μV)	P	30.2 (4.8)	17.2* (3.7)	10.3* (2.4)	7.3* (1.8)	20.6* (3.1)	19.8* (2.7)
	A	33.8 (4.9)	19.7* (3.3)	16.6* (3.9)	13.6* (3.4)	22.0* (4.2)	23.6* (3.8)
	PA	24.4 (2.9)	7.9*† (1.0)	6.8* (1.6)	3.5* (0.6)	16.1* (2.2)	24.0 (3.9)

WO1 and 2 = washout 1 (60 min) and washout 2 (120 min); P = propofol; A = alfentanil; PA = propofol/alfentanil.

* $P < 0.05$ versus baseline.

† $P < 0.05$, P versus PA.

to pain caused by electrical stimulation of tooth pulp, or the finger and toe.^{12,18} The models appear to provide reproducible results that correlate with known analgesic effects of opioids in clinical practice.¹² Thus, it is likely that the results are predictive of the clinical actions of the propofol/alfentanil combination in clinical situations.

Evoked potential responses were initially intended to provide an objective assessment of pain. However, during propofol infusion, evoked potential amplitude was reduced out of proportion to changes in the subjective pain report as has been observed with benzodiazepines and ethanol.²⁹ Thus, evoked potential amplitude may be an unreliable indicator of the perception of pain in the presence of propofol and other sedative hypnotic agents.

This study highlights propofol's ability to offset the emetic symptoms that accompanied alfentanil infusion in 50% of subjects, an observation that is consistent with clinical reports that postoperative nausea and vomiting are less commonly observed after propofol anesthesia than after anesthesia induced by other agents.^{2,30-32} It also supports the report by Borgeat *et al.* that propofol temporarily relieves symptoms of postoperative nausea/vomiting at subsedative doses.³³ The site of action of the antiemetic effect of propofol remains unknown, but one hypothesis postulates blockade of dopaminergic receptors in the brain.³⁴

Propofol failed to prevent or diminish pruritus, another known side effect of opioids that occurred in the majority of subjects during alfentanil infusion. Ballantyne *et al.* suggest that opioids rarely cause pruritus when administered parenterally (1%), but frequently do so when administered into the epidural (8%) or intrathecal spaces (43%).³⁵ Our observations suggest

that parenteral opioids commonly produce pruritus, and that when prospective studies are carefully done, these effects are readily discernible. The high incidence of pruritus associated with alfentanil administration is consistent with reports by Hill *et al.*, who demonstrated a similar incidence in human subjects undergoing steady-state infusions of alfentanil, fentanyl, and morphine.¹² Of interest, Borgeat recently reported that pruritus caused by intrathecal or epidural morphine was readily abolished for a brief duration by propofol at small doses that did not induce sedation. In our study, propofol clearly had no effect on the pruritus caused by intravenous infusion of alfentanil.³⁶ The disparity between these observations suggests that pruritus accompanying intrathecal or epidural opioids is mediated by a different mechanism than that which occurs with parenteral opioids. Thus, propofol might block effects of opioids at the spinal level through inhibitory effects on dorsal horn spinal cord transmission,^{35,36} but have no effect on supraspinal mediation of pruritus.

In summary, the results of this study demonstrate:

1. There is a pharmacokinetic interaction between propofol and alfentanil when administered simultaneously that leads to increased plasma propofol and alfentanil concentrations.
2. Propofol sedation is enhanced by co-administration of alfentanil.
3. Ventilation is minimally depressed by sedative doses of propofol. When combined with alfentanil, depression of ventilation occurs that is greater than that observed with either drug alone, but the net effect on end-tidal carbon dioxide is not different from the effects of alfentanil alone.
4. Propofol enhances opioid analgesia at plasma concentrations that cause a moderate degree of sedation.

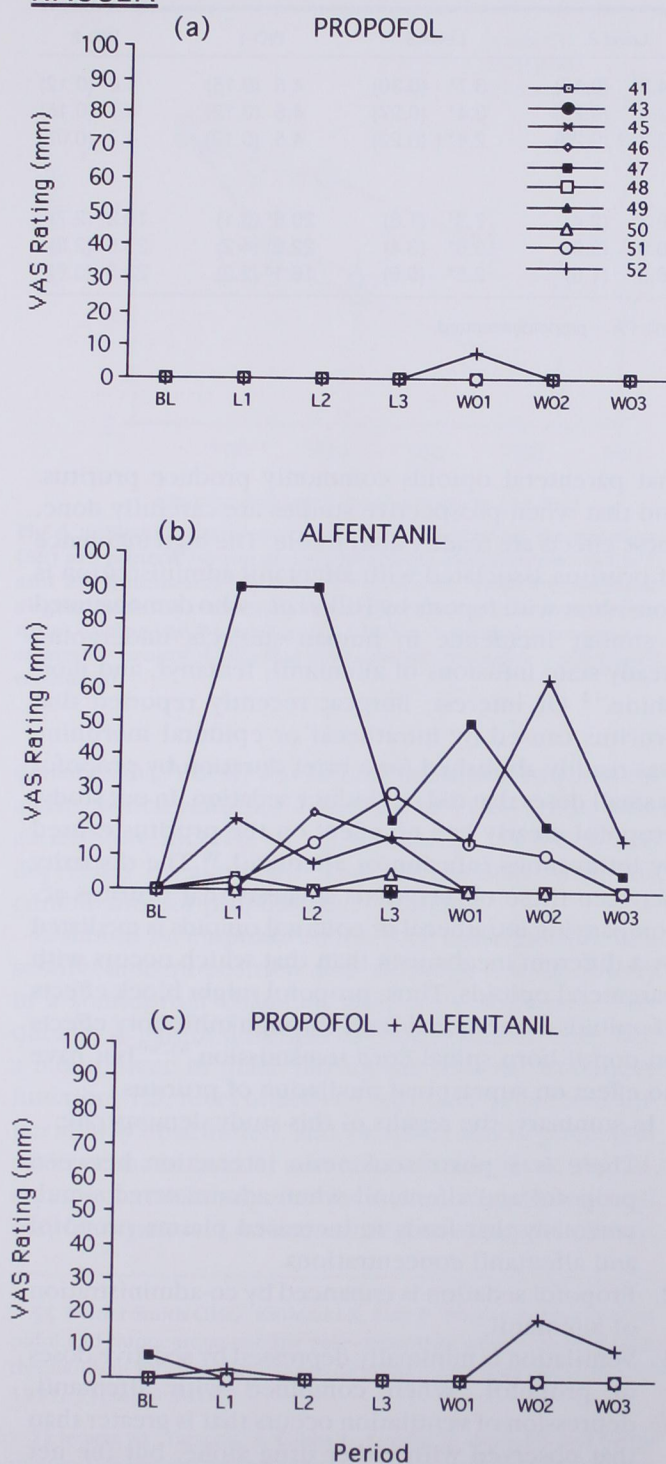
NAUSEA

Fig. 7. Nausea rating by individual subjects by visual analog scale (0–100 mm), during propofol treatment (A), alfentanil treatment (B), and propofol/alfentanil treatment (C). BL = pre-drug; L1–L3 = infusion levels 1–3; W01–3 = washout periods at 40, 80, and 120 min.

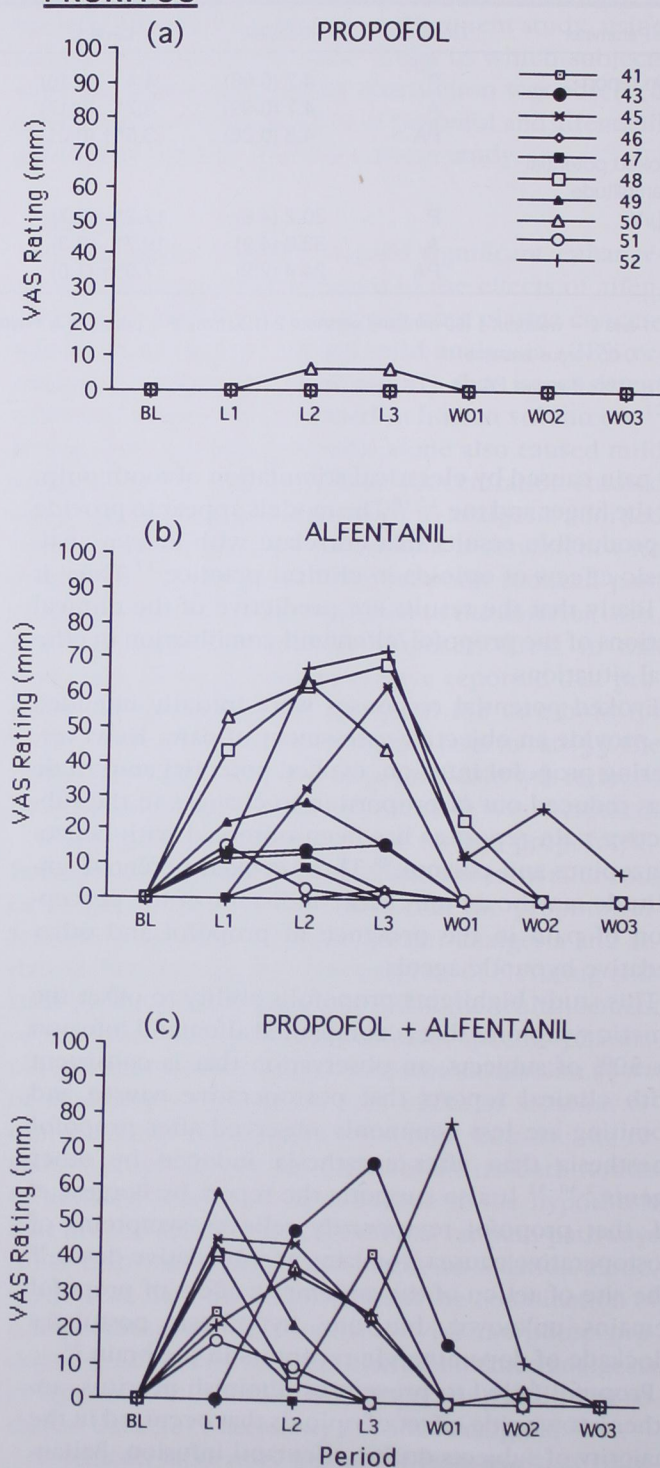
PRURITUS

Fig. 8. Pruritus rating by individual subjects by visual analog scale (0–100 mm), during propofol (A), alfentanil (B), and propofol/alfentanil treatment (C). BL = pre-drug; L1–3 = infusion levels 1–3; W01–3 = washout period at 40, 80, and 120 min.

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5. Sedative doses of propofol oppose opioid-induced emetic symptoms, but not opioid-induced pruritus.

In general, the combined use of alfentanil and propofol appears to offer multiple advantages over either drug alone with the one exception that ventilation is impaired by the presence of the opioid.

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