Alfentanil and Placebo Analgesia

No Sex Differences Detected in Models of Experimental Pain

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Background: To assess whether patient sex contributes to the interindividual variability in alfentanil analgesic sensitivity, the authors compared male and female subjects for pain sensitivity after alfentanil using a pharmacokinetic–pharmacodynamic modeling approach.

Methods: Healthy volunteers received a 30-min alfentanil or placebo infusion on two occasions. Analgesia was measured during the subsequent 6 h by assaying tolerance to transcutaneous electrical stimulation (eight men and eight women) of increasing intensity or using visual analog scale scores during treatment with noxious thermal heat (five men and five women). Sedation was concomitantly measured. Population pharmacokinetic–pharmacodynamic models were applied to the analgesia and sedation data using NONMEM. For electrical pain, the placebo and alfentanil models were combined *post hoc*.

Results: Alfentanil and placebo analgesic responses did not differ between sexes. The placebo effect was successfully incorporated into the alfentanil pharmacokinetic–pharmacodynamic model and was responsible for 20% of the potency of alfentanil. However, the placebo effect did not contribute to the analgesic response variability. The pharmacokinetic–pharmacodynamic analysis of the electrical and heat pain data yielded similar values for the potency parameter, but the blood–effect site equilibration half-life was significantly longer for electrical pain (7–9 min) than for heat pain (0.2 min) or sedation (2 min).

Conclusions: In contrast to the ample literature demonstrating sex differences in morphine analgesia, neither sex nor subject expectation (*i.e.*, placebo) contributes to the large between-subject response variability with alfentanil analgesia. The difference in alfentanil analgesia onset and offset between pain tests is discussed.

ALL anesthesiologists are aware of the large between-patient variability in the intended and adverse effects of most drugs they use in clinical practice. To achieve optimal anesthesia and (postoperative) analgesia, it is important to gain knowledge regarding those variables that contribute to this variability. An increasing number of experimental and clinical studies have demonstrated the importance of subject and patient sex in the variability of drug-induced anesthesia. For example, recent studies have shown that sex has a significant influence on propofol–alfentanil anesthesia sleep time (with faster emergence in women) and on morphine analgesia.[1,2]

Morphine-linked sex differences are related to differences in morphine pharmacodynamics with greater morphine potency in women, whereas the sex differences in recovery from general anesthesia may have both pharmacokinetic and pharmacodynamic origins. Here, we expand our knowledge on the effect of sex on opioid analgesia. We studied the influence of sex on alfentanil analgesia in a group of healthy young volunteers using a pharmacokinetic–pharmacodynamic modeling approach; analgesia was measured using an experimental transcutaneous electrical pain model used previously.[2] Our main objective was whether the increased opioid potency in women previously observed for morphine and certain κ-opioid receptor agonists also applies to alfentanil, a widely used selective μ-opioid receptor agonist. A second objective was to examine whether placebo responses could explain some of the variability in alfentanil responses. The placebo effect is a complex phenomenon that consists of many subjective components (*e.g.*, expectation, memory and experience, attention, suggestion, and conditioning) and physiologic components (related to the activation of opioid and nonopioid analgesic pathways).[3,4] The influence of the placebo response on opioid analgesia is seldom examined. To do so, we incorporated the observed placebo responses in the pharmacokinetic–pharmacodynamic modeling of alfentanil. In addition to sex, opioid analgesic responses have also been shown to vary with pain type.[5,6] That is, a given opioid may be more effective against particular nociceptive modalities than others, an effect that may be genetically determined.[6] In addition, sex and gender pain differences vary with pain modality.[7] Therefore, as a final aim, we compared alfentanil analgesia against transcutaneous electrical pain, as characterized by our pharmacokinetic–pharmacodynamic model, with another pain modality, noxious heat, as well as on opioid-induced sedation.

Materials and Methods

Subjects and Apparatus

Thirty-six healthy volunteers (18 men and 18 women, aged 18–28 yr, body mass index < 28 kg/m^2) were recruited after approval of the protocol by the local Human Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands) and provided oral and written consent. All female volunteers were taking oral contraceptives. Subjects were asked to have a normal night of sleep and not to eat

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130

or drink for at least 6 h before the study. They were comfortably seated in a hospital bed for the duration of the studies.

Design of the Studies

Pain (Studies 1 and 2). We used two distinct pain models to test the pharmacodynamics of alfentanil.

Study 1: Transcutaneous Electrical Stimulation. In 16 volunteers (8 men and 8 women) we determined the influence of a 30-min infusion of alfentanil and placebo on pain tolerance induced by transcutaneous electrical stimulation (TES) during a 5-h period, using a randomized, double-blind, crossover design. The sample size was determined on the basis of the results on our previous study on morphine with $\alpha = 0.01$ and $\beta = 0.8$.[2] In an additional group of 10 subjects (5 men and 5 women) we tested the effect of no drug on the development of pain tolerance during a 5-h period.

Transcutaneous electrical stimulation was applied to the skin overlying the tibial bone (shin bone) of the left leg *via* two surface electrodes (Red Dot; 3M, London, Ontario). The electrodes were attached to a computer interfaced constant current stimulator, which was locally designed and constructed. The intensity of the noxious stimulation was increased from 0 mA in steps of 0.5 mA per 1 s with a pulse duration of 0.2 ms at 10 Hz (cutoff = 128 mA). The subjects were instructed to press a button on a control box when no further increase in stimulus intensity was acceptable to them (pain tolerance). When the subject pressed the button, the stimulus train ended, and the current was collected and stored on the hard disc of a computer for further analysis. Before the studies, the subjects were trained for approximately 1 h, during which several stimulus trains were applied. These data were discarded. Next, baseline values were obtained in triplicate. The averaged baseline value was used in the data analysis.

Study 2: Thermal Pain. The effect of a 30-min infusion of alfentanil and placebo on the visual analog scale (VAS) score in response to a painful heat stimulus was assessed in 10 subjects (5 men and 5 women). The VAS value was scored by the subjects on a 10-cm paper scale that ranged from 0 (no pain) to 100 (worst possible pain). Heat pain was induced using the TSA-II device (Medoc Ltd., Ramat Yishai, Israel) running WinTSA 5.32 (-10) software (Medoc Ltd.). Using a 3-cm² Peltier element or thermode, the skin of the volar side of the left forearm was stimulated with a gradually increasing stimulus (0.5°C/s). The baseline temperature was set at 32°C. After the subjects were familiarized with the device and the VAS scoring, the VAS score to three heat stimuli was assessed with the following peak temperatures: 46°, 48°, and 49°C. The stimulus causing a VAS score greater than 55 mm was used in the remainder of the study. The test data were discarded. Next, baseline values were obtained in triplicate. The averaged baseline value was used in the data

analysis. The volar side of the arm was divided into six zones and marked as previously described.[8] The thermode was moved from zone to zone between stimuli.

Studies 1 and 2. During and after drug infusion, pain assessments were made at regular intervals at times t = 5, 9, 15, 19, 25, 29, 33, 38, 43, 48, 53, 60, 70, 75, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 240, 270, and 300 min after the start of the drug infusion. A similar time schedule was applied in the no-drug study.

Subjects participating in the drug studies were tested twice, with at least 3 weeks between the alfentanil and placebo arms of the study. Drugs were presented to subjects in a randomized and blinded order.

Sedation (Study 3). In addition, we assessed the effect of alfentanil on sedation in all 16 subjects participating in the TES study. They were queried at regular intervals (t = 0, 5, 15, 25, 35, 45, 60, 75, 90, 120, 150, 180, 210, 240, and 300 min) regarding the magnitude of sedation by means of a visual rating scale from 0 to 9 (0 equals no sedation and 9 equals the feeling that occurs just before falling asleep).

Alfentanil Infusion and Blood Sampling

After arrival in the research unit, an arterial line for blood sampling was placed in the left or right radial artery during local anesthesia. In the contralateral arm, an intravenous line was inserted for drug infusion. Placebo (0.9% NaCl in water) or alfentanil (Janssen-Cilag BV, Tilburg, The Netherlands; alfentanil HCl, 0.9% NaCl in water) infusion commenced at 10:00 AM using a target-controlled infusion. A Psion palm-top computer (London, England) programmed with the population pharmacokinetic data set reported by Maitre *et al.*[9] was connected to a Becton Dickinson infusion pump (St. Etienne, France), which contained either alfentanil (0.25 mg/ml) or saline. The subjects were infused for 30 min. The infusion was such that the target plasma concentrations of alfentanil (C_{target}) and placebo were 50 ng/ml from t = 0 to t = 10 min, 100 ng/ml from t = 10 to t = 20 min, and to 150 ng/ml from t = 20 to t = 30 min. Time t = 0 was the start of the infusion.

In the drug studies, blood sampling took place at times t = −10, 3, 5, 9, 13, 15, 19, 23, 25, 29, 31, 33, 35, 38, 43, 53, 60, 75, 90, 120, 150, 180, 240, and 300 min. In instances where blood sampling coincided with pain assessment, the pain test preceded the sampling. Plasma was separated within 15 min of blood collection and centrifuged for 10 min at 3,500 min⁻¹. Plasma samples were immediately stored at −25°C until analysis. Plasma alfentanil concentrations were determined by capillary gas chromatography, as previously described, with some minor modifications. A sample of 0.5 ml plasma was used and was extracted with 5 ml pentane Baker Ultra-resianalyzed Baker No. 9333. The operating temperature of the column oven was 215°C, and the flow rate of the

carrier gas (helium) was 6 ml/min. The coefficient of variation of this method was lower than 3% in the concentration range of this study.

Pharmacokinetic–Pharmacodynamic Data Analysis

The population pharmacokinetics and pharmacodynamics of alfentanil were determined sequentially with NONMEM version V, level 1.1 (software for nonlinear mixed effects modeling; University of California, San Francisco, California; 1999).[10]

Alfentanil Pharmacokinetic Model. The alfentanil infusion rates were obtained from the log files of the target-controlled infusion device and used as input of a standard pharmacokinetic model, which consisted of either two or three compartments to assess how the alfentanil concentration data were best described. The pharmacokinetic parameters (volumes and clearances) were assumed to be lognormally distributed across the population.

Alfentanil Pharmacodynamic Data Analysis. To eliminate a possible hysteresis between opioid plasma concentrations, as described by the pharmacokinetic model, and analgesic effect, an effect compartment was postulated. This effect compartment equilibrates with the plasma compartment with a half-life $t_{1/2}k_{e0}$ (blood–effect site equilibration half-life).

The response to the electrical noxious stimulation (identifying pain tolerance) was modeled by assuming that alfentanil attenuates the response to the stimulus by inhibition of signal propagation or central processing or both. As a consequence, stronger stimuli are needed before the subject presses the pain tolerance button. The attenuation (A) was described by an inhibitory sigmoid Emax model[2]:

$$A = [1 + (Ce(t)/AC_{50})^\gamma]^{-1}, \quad (1)$$

where $Ce(t)$ is the alfentanil effect site concentration, AC_{50} is the effect site concentration causing 50% attenuation, and γ is a dimensionless shape parameter. Because a response of the subject occurs when his or her pain sensation exceeds the response threshold for pain tolerance, we use equation 2 for the current at time t, E(t):

$$E(t) = E_0 \cdot [1 + (Ce(t)/AC_{50})^\gamma], \quad (2)$$

where E_0 is the baseline or predrug current.

The VAS score in response to heat pain was modeled as follows:

$$\text{VAS(t)} = (\text{VAS at baseline}) \cdot A = (\text{VAS at baseline}) \cdot [1 + (Ce(t)/AC_{50})^\gamma]^{-1}, \quad (3)$$

where VAS(t) is the observed VAS score at time t and VAS at baseline is the predrug VAS score.

For sedation, the probability of observing a sedation score greater than k (k ranges from 0 to 8) is assumed to be[11]

$$P(\text{sedation score} > k) = Ce^\gamma(t)/(Ce^\gamma(t) + C_k^\gamma), \quad (4)$$

where C_k is the concentration where P(sedation score > k) = 0.5. The C_k values for k > 1 were parametrized by $C_k = C_{k-1} \cdot [1 + \theta_k \cdot \exp(\eta_k)]$, which allows incorporation of interindividual variability while guaranteeing that C_k is an increasing function of k. The probability of observing sedation score k is then given by P(sedation score > k) − P(sedation score > k − 1) and P(sedation score = 0) = 1 − P(sedation score > 0). The likelihood of observing the set of sedation scores was maximized (using NONMEM) to estimate the model parameters.

Placebo and Combined Alfentanil–Placebo Data Analysis. For the electrical pain data, the following placebo model was designed, consisting of two parts, an increasing part and a decreasing part:

$$EP(t) = E_0 \cdot P(t) = E_0 \cdot \frac{1 + M \cdot (1 - e^{-\alpha t})}{1 + M' \cdot (1 - e^{-\beta t})}, \quad (5)$$

where EP(t) is the placebo response, E_0 is the baseline (= predrug) current, and P(t) is the placebo effect; its denominator and numerator allow for an increasing and/or decreasing effect, respectively. M and M′ are the magnitude of the increasing/decreasing placebo effect, and α and β are time constants of these effects, respectively. The magnitude M is equal to the magnitude M′, but in this model, both magnitudes can differ individually because the interindividual variability (η values) were allowed to be different for M and M′.

Alfentanil and placebo components were combined in an additive fashion:

$$E(t) = E_0 \cdot [(Ce(t)/AC_{50})^\gamma + P(t)], \quad (6)$$

where P(t) is given in equation 5. The placebo parameters determined from the placebo data analysis were fixed in the combined model.

Statistical Analysis. The pharmacokinetic and pharmacodynamic models were fitted to the data with NONMEM. The interindividual variability of the parameters was described by using an exponential variance model:

$$\theta_{\text{individual}} = \theta_{\text{typical}} \cdot \exp(\eta_i), \quad (7)$$

where η_i is the interindividual variability term, θ_{typical} is the population parameter, and $\theta_{\text{individual}}$ is the individual parameter value. The intraindividual variability was described by a proportional error model for the pharmacokinetic data and an additive error model for the pharmacodynamic data (except for sedation); the SD of the residual error (σ) was allowed to vary interindividually according to equation 7. To determine whether some biologic factors may explain the analgesic response variability, we tested the following factors (covariates): sex, age, weight, and lean body mass. They were included by allowing different parameter values for binary covariates

Fig. 1. Alfentanil and placebo analgesic responses assessed by using two distinct pain models (transcutaneous electrical pain: *A–C*; thermal pain: *D–F*) and alfentanil- and placebo-induced sedation (*G–I*). Top graphs (*A*, *D*, and *G*) are the mean alfentanil plasma concentrations ± 95 confidence intervals (CIs); middle graphs are the mean alfentanil responses ± 95% CIs (*B*: electrical pain; *E*: thermal pain; *H*: sedation); bottom graphs are the mean placebo responses ± 95% CIs (*C*: electrical pain; *F*: thermal pain; *I*: sedation). Pain tolerance values (electrical pain model) are relative to baseline. C_P = plasma concentration; Num. = numerical; VAS = visual analog scale score.
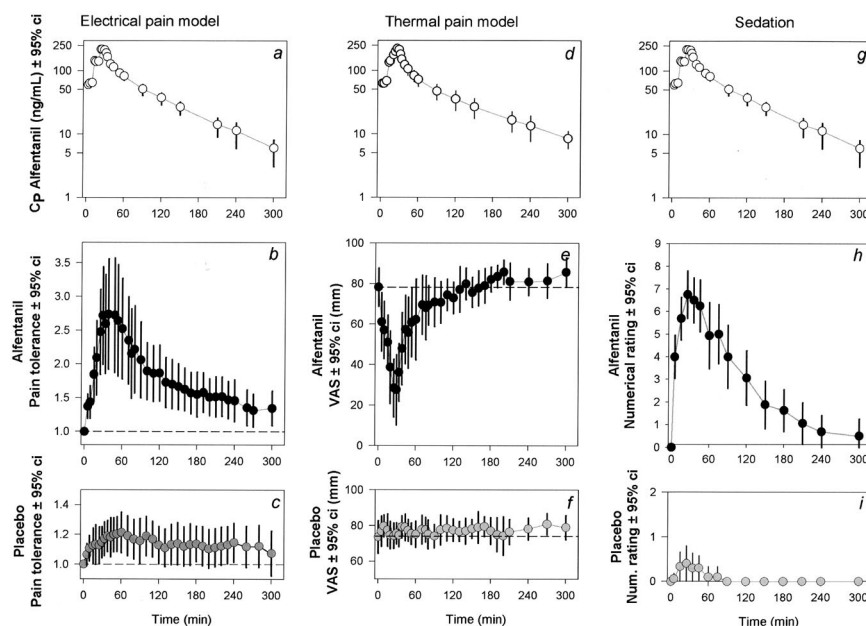
and a dependence *via* a power law for continuous variables, *e.g.*, for volume 1:

$$V_1 = V_1(\text{population}) \cdot (\text{weight/median weight})^\alpha. \quad (8)$$

Model selection was done on the basis of the log likelihood criterion ($-2LL$; a decrease of more than 6.6 is significant at the $P < 0.01$ level for one additional parameter) and visual inspection of the fits. Besides visual inspection, the goodness of fit was also assessed by the coefficient of determination (R^2).

Results

Alfentanil Pharmacokinetics

Figures 1A, D, and G show the average measured alfentanil concentrations. The pharmacokinetic model parameters are collected in table 1. A three- rather than a two-compartment model best described the pharmacokinetic data. For none of the model parameters did inclusion of the covariates (sex, age, weight, height, and

Table 1. Population Pharmacokinetic Model Parameter Estimates

	Value	SE	%CV
V_1	4.32	0.663	—
V_2	4.91	0.726	29
V_3	12.2	0.836	28
Cl_1	0.274	0.0182	32
Cl_2	1.33	0.342	54
Cl_3	0.307	0.0262	—
σ^2	0.009	0.002	52

— = parameter not included in the statistical model; $Cl_{1–3}$ = clearances of compartments 1–3 (in liters per minute); %CV = percent coefficient of variation; σ^2 = SD of the residual error (within-subject variability); $V_{1–3}$ = volumes of compartments 1–3 (in liters).

lean body mass) improve the model fits ($P > 0.01$). Inspection of the individual data fits (see figs. 2 and 3 for examples) showed that the pharmacokinetic model adequately described the alfentanil data as further quantified by the median of the weighted residuals and median of the absolute weighted residuals, which were -0.232% and 4.26%, respectively. On average, our target-controlled infusion caused $40–50\%$ greater alfentanil concentrations than predicted by the Maitre kinetic set.

Alfentanil and Placebo Pharmacodynamics

The alfentanil and placebo analgesic and sedation responses are given in figure 1. Alfentanil and placebo produced a significant increase in pain tolerance as derived from the electrical pain test. The maximum pain tolerance values ± SDs observed were 2.71 ± 1.38 and 1.29 ± 0.30 relative to baseline for alfentanil and placebo (panels B and C). The values were reached at times $t = 48$ and 60 min, respectively. In the heat pain test, alfentanil caused a significant reduction in VAS score from 80 ± 5 mm to 29 ± 10 mm at $t = 29$ min (panel E). In contrast, placebo VAS values did not change over time (panel F). Alfentanil but not placebo produced significant sedation (average maximum score = 6.8 ± 2.1 at $t = 25$ min; panels H and I).
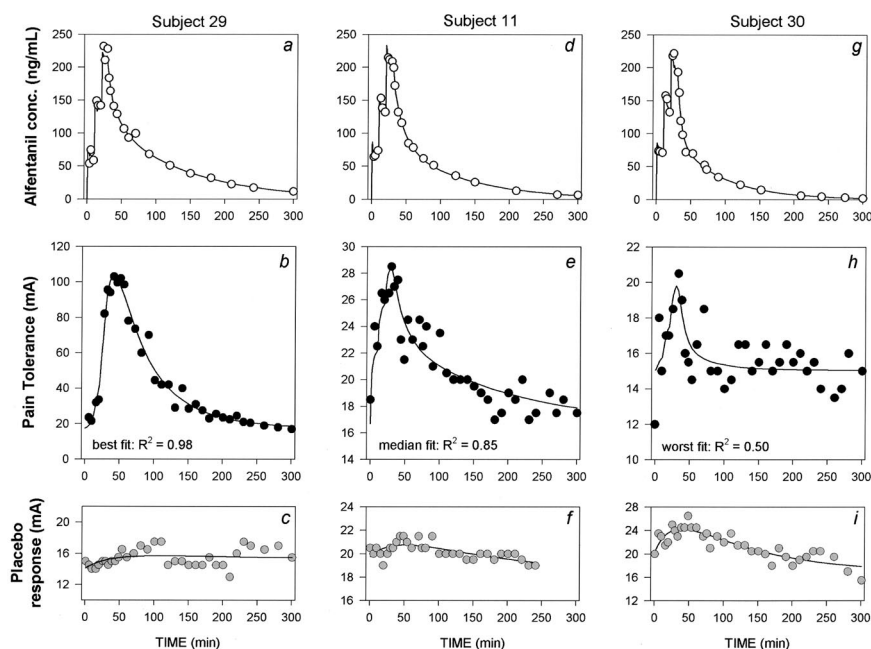
Study 1: Transcutaneous Electrical Stimulation. The results of the pharmacodynamic analysis are summarized in tables 2 and 3. In figure 2, best, median, and worst alfentanil pharmacodynamic data fits are plotted (panels B, E, and H) together with the corresponding placebo fits (panels C, F, and I). The alfentanil $t_{1/2}k_{e0}$ and AC_{50} were 9 min (95% approximate confidence interval [CI], $4–14$ min) and 133 ng/ml (95% approximate CI, $73–193$ ng/ml), respectively. Parameter γ could be fixed to a value of 1 without significant deterioration of the fit.

Fig. 2. Influence of alfentanil and placebo on electrical pain tolerance in three subjects. Best, median, and worst data fits are given for the acute tolerance data fits (*B*, *E*, and *H*). Corresponding measured alfentanil plasma concentrations (conc.) and pharmacokinetic data fits (*A*, *D*, and *G*) and placebo responses and data fits (analyzed with the placebo model; *C*, *F*, and *I*) are included.

The placebo analgesic response varied in time course and magnitude among subjects; some subjects showed a predominant increasing placebo response, whereas others showed an increasing response followed by a decreasing component (fig. 2). The population analysis indicated that there was a significant analgesic placebo response (table 3), which was in magnitude approximately one fifth of the alfentanil analgesic response. The parameters obtained from the separate placebo analysis could be fixed in the combined model without a significant decrease of $-2LL$. Fixing the placebo parameters and subsequently restricting the analysis to the alfentanil set provided stability in the combined model. Combining responses yielded a reduced alfentanil potency and reduced $t_{1/2}k_{e0}$ by approximately 20%: AC_{50} (typical value ± SE [%CV], 95% approximate CI) = 164 ± 41 [72%], 84–244 ng/ml; $t_{1/2}k_{e0}$ = 7.1 ± 2.0 [76%], 5.1–9.1 min. Fixing parameter γ to a value of 1 had no significant effect on the data fits.

For all three performed analyses, none of the tested covariates caused an improvement of the model fits at the $P < 0.01$ level. This indicates that alfentanil and placebo responses did not differ between men and women. See also the averaged male and female analgesic responses to TES ± 95% CIs in figure 3.

In 9 of the 10 subjects participating in the no-drug study, the current at which pain tolerance was reached did not differ over time (currents at t = 0, 60, 120, 180, 240, and 300 min: 19.1 ± 4.4, 20.4 ± 6.3, 21.1 ± 7.4, 18.6 ± 5.8, and 18.5 ± 8.3 mA, respectively [values are mean ± SD; analysis of variance: not significant]). The mean coefficient of variation was 8.3%. In one subject, a linear increase in current was observed from 14.5 mA (t = 0) to 28.5 mA (t = 300 min).

Study 2: Thermal Pain. The results of the pharmacodynamic analysis are summarized in table 2. In figure 4, best, median, and worst alfentanil pharmacodynamic data fits are plotted (panels B, D, and F). The parameter estimates were as follows: $t_{1/2}k_{e0}$, 0.2 min (95% approxi-
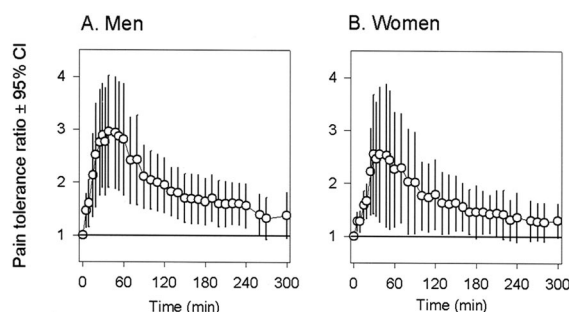
Fig. 3. Male (*A*) and female (*B*) alfentanil analgesic responses to transcutaneous electrical stimulation. Values are mean ± 95% confidence intervals (CIs). Note the very large response variability in both sexes. There were no differences in analgesic effect between the two sexes.

Table 2. Modeling Analgesia: Population Pharmacodynamic Model Parameter Estimates

	Electrical Pain			Heat Pain		
	Value	SE	%CV	Value	SE	%CV
Baseline*	18.1	2.06	9	82	2.9	10
$t_{1/2}k_{e0}$, min	9.07	2.55	68	0.20	0.14	362
AC_{50}, ng/ml	133	31.7	52	141	29.7	67
γ	1	—	33	2.0	0.25	—
σ^2	4.85	1.88	37	72.7	18.7	38

* Baseline units: milliamperes for electrical pain and millimeters for heat pain.
— = parameter not included in the statistical model; AC_{50} = effect site concentration causing 50% increase attenuation of nociception; CV = percent coefficient of variation; γ = shape parameter; σ^2 = variance of the residual; $t_{1/2}k_{e0}$ = blood–effect site equilibration half-life.

Table 3. Modeling the Placebo Effect: Population Parameter Estimates

	Value	SE	%CV
Baseline, mA	19.6	2.1	42
M	0.75	0.06	—
M′	0.75	—	54
α, min^{-1}	0.021	0.005	80
β, min^{-1}	0.009	0.002	71
σ^2	1.73	0.52	59

— = not included in the statistical model; α = time constant of the analgesic effect of the placebo response; β = time constant of the algesic effect of the placebo response; %CV = percent coefficient of variation; M = magnitude of the analgesic part of the placebo response; M′ = magnitude of the algesic part of the placebo response; σ^2 = SD of the residual error (within-subject variability).

mate CI, 0–0.4 min); AC_{50}, 141 ng/ml (95% approximate CI, 81–201 ng/ml); and γ, 2.0 (95% approximate CI, 1.5–2.5). None of the tested covariates caused an improvement of the model fits. An interesting observation was that 8 of the 10 subjects showed some period of hyperalgesia after termination of the alfentanil infusion (VAS score > baseline; see fig. 4 for examples).

Study 3: Sedation. The scoring system (ranging from 0 to 9) enabled the adequate description of the subjective feelings related to alfentanil-induced sedation (scores were made over the whole range of levels). None of the subjects fell asleep during the study, and all were able to complete the scoring. Randomly selected examples of data fits of five subjects are shown in figure 5. Visual inspection showed that the model adequately described the data. Model parameter estimates are given in table 4. The value of $t_{1/2}k_{e0}$ was 2.2 min (95% approximate CI, 0–4 min). The alfentanil concentration causing 50% effect (or a sedation score between levels 4 and 5) was approximately 75 ng/ml. C_k values indicate the alfentanil concentration at which the probability of observing a sedation score greater than k was 50%. For example, the probability of a sedation score greater than 8 (*i.e.*, 9) was 50% at an alfentanil plasma concentration of 296.4 ng/ml (C_k = 8). Figure 5 shows the probability of the occurrence of sedation scores 0–9 as a function of alfentanil effect site concentration. The large overlap among sedation scores is apparent. Some scores never reach the highest probability (scores 1 and 2) and hence are not likely to occur at any alfentanil concentration.

Electrical Pain–Thermal Pain–Sedation. In figure 6, we plotted the steady state data for the three endpoints of our studies. Parameter A in plots A and B denote the attenuation of the response sensitivity to the noxious stimulus by alfentanil (see equation 1). The shape of the response curves is for all three measures

comparable with similar alfentanil potency observed for electrical and thermal pain. To visually compare the delays in effect and verify the results of the pharmacokinetic–pharmacodynamic analysis, we plotted the population averages of the measured plasma alfentanil concentration *versus* the three measured effects (fig. 7). For electrical pain, a wide clockwise hysteresis loop with maximum effect occurred when the plasma concentration decreased to 100 ng/ml (fig. 7A).

Using a nonparametric loop collapsing approach on the data set of all individuals participating in study 1 yielded a $t_{1/2}k_{e0}$ (mean [median] ± SEM) of 11.3 [8.3] ± 2.1 min.* For heat pain, little to no hysteresis was observed, and a small counterclockwise hysteresis was apparent. For sedation, a small clockwise loop indicating a small delay was visible.

Discussion

We used a pharmacokinetic–pharmacodynamic modeling approach to compare the analgesic effect of the μ-opioid receptor agonist alfentanil in males and females. The main findings of our study are as follows: (1) Alfentanil is an equipotent analgesic in men and women; (2) placebo analgesic responses do not differ between men and women; (3) the placebo effect is successfully incorporated in the alfentanil pharmacokinetic–pharmacodynamic model and is responsible for 20% of the potency of alfentanil; however, the placebo effect does not critically contribute to the analgesic response variability; and (4) the pharmacokinetic–pharmacodynamic analysis of the transcutaneous electrical and heat pain data yields similar values for the potency parameter AC_{50}, but the $t_{1/2}k_{e0}$ is significantly greater when derived from electrical pain (7–9 min) than from heat pain (0.2 min). The smaller value of $t_{1/2}k_{e0}$ corresponds with the small delay observed from sedation measurements (2 min).

Sex Differences

There is ample evidence from animal and human studies for the existence of sex differences in opioid-induced analgesia and adverse effects.[2,7,12–18] Approximately 70% of recent studies on opioid-induced analgesia in humans observed sex differences, with greater analgesia typically observed in women.[19] Discrepancies between studies may be related to the specific drug tested, dose, route of administration, pain modality, hormonal status of the subjects, and experimental design. Previously, we assessed the effect of sex on morphine analgesia in a study of similar size and in a population similar to the current one (young, healthy volunteers) using transcutaneous electrical stimulation.[2] We observed greater analgesic responses in women relative to men, which were related to sex differences in the pharmacodynamics of mor-

* Using ke0obj, written by Dr. S. L. Shafer (Stanford University, Palo Alto, California). Available at: http://anesthesia.stanford.edu/pkpd. Accessed June 24, 2004.
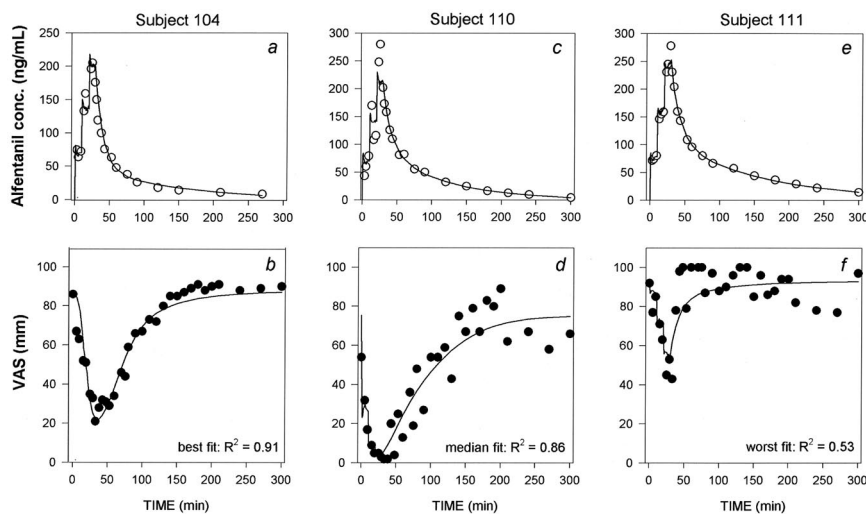
Fig. 4. Influence of alfentanil on the visual analog scale score (VAS) using the thermal pain model in three subjects. Best, median, and worst fits are given for the VAS data fits (*B*, *D*, and *F*). Corresponding measured alfentanil plasma concentrations (conc.) and pharmacokinetic data fits (*A*, *C*, and *E*) are included.

phine and not to differences in pharmacokinetics. Our current data on alfentanil contrast with the observations made for morphine. Multiple factors may be involved in the difference between the current findings and our

Fig. 5. (*A*) Probability of sedation scores 0–9 (0 = fully awake; 9 = maximal sedation) as a function of the alfentanil plasma concentration. The sedation scores 0–9 are given in the figure and correspond to the lines with increasing peak concentrations. (*B*) Examples of the sedation data fits of five randomly selected subjects (subject numbers are shown). The sedation scale ranged from 0 (= fully awake) to 9 (= maximal sedation) as scored by the subjects themselves.

previous findings. Previously, we used transcutaneous electrical stimulation at a stimulus frequency of 1 Hz *versus* 10 Hz in the current study. Different stimulus frequencies may activate different pain pathways, which then may vary in their sensitivity to sex differences. In contrast to our current design, subjects were previously asked to state at which point they experienced pain tolerance. Although we took great care to avoid any bias (*e.g.*, subjects were queried by same-sex researchers), we are unable to exclude this factor. However, our previous findings are in accord with other studies on sex-related differences in morphine analgesia (and side effects) and clinical findings for greater morphine analgesia in women.[14,15,19,20] Apart from methodologic issues, the difference in study outcomes may be related to specific pharmacologic differences between alfentanil and morphine (*e.g.*, recruitment of different G proteins at the inner layer of the cell membrane). Further studies are needed to explain the important and clinically relevant difference in behavior of various μ opioids in men and women.
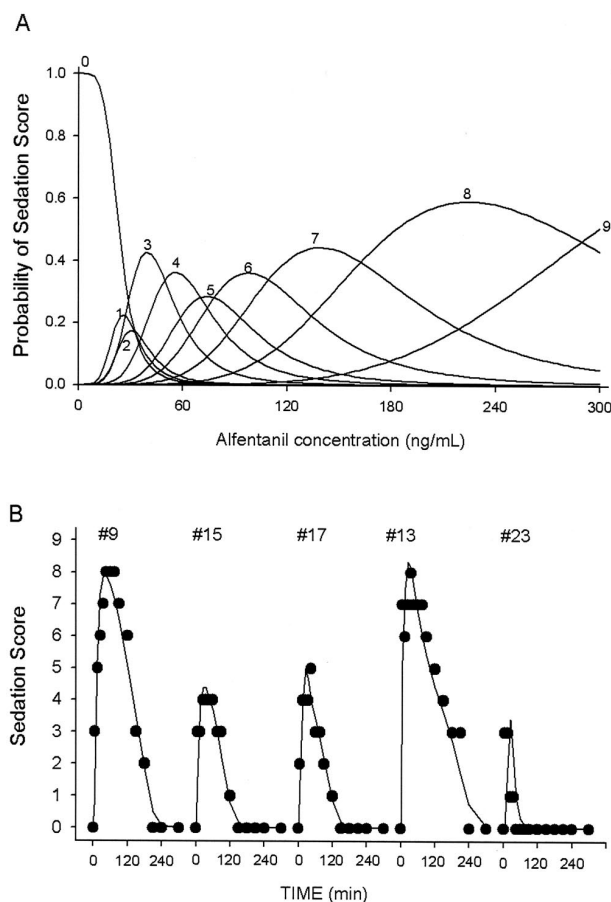
Table 4. Modeling Sedation: Population Pharmacodynamic Model Parameter Estimates

	Value	SE	%CV	C_k
$t_{1/2}k_{e0}$, min	2.18	1.43	118	
γ	4.83	0.403	—	
C_0, ng/ml	23.4	4.11	—	23.4
θ_1	0.210	0.077	—	28.3
θ_2	0.158	0.067	—	32.8
θ_3	0.460	0.104	—	47.8
θ_4	0.369	0.099	95	65.5
θ_5	0.275	0.085	—	83.5
θ_6	0.368	0.065	—	114.2
θ_7	0.484	0.136	—	168.7
θ_8	0.757	0.247	—	296.4

— = parameter not included in the statistical model; C_k = concentration where P(sedation level > k) = 0.5 and $C_k = C_{k-1} \cdot (1 + \theta_k)$; %CV = percent coefficient of variation; γ = shape parameter; $t_{1/2}k_{e0}$, blood–effect site equilibration half-life.

Fig. 6. Steady state relations of the influence of alfentanil on electrical pain, heat pain, and sedation. On the y-axis, parameter A (see equation 2; *A* and *B*) is given for both pain measures and expected sedation level is given for sedation (*C*). C_e = effect concentration.
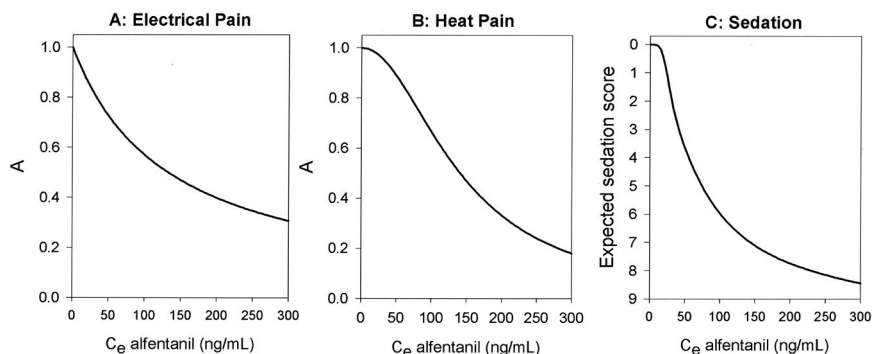
The Placebo Effect

Potential causes (apart from sex) for the large analgesic response variability are psychological factors such as patient (or, in this study, subject) expectations, experiences, suggestion, and conditioning. These phenomena play an important role in the development of an analgesic (or hyperalgesic) response to placebo.[3,4,21-23] For example, Amanzio *et al.*[4] showed that after pharmacologic blockade of the placebo response with naloxone or after hidden opioid injections, the variability and effectiveness of the analgesic response were decreased. We performed a simultaneous analysis of the alfentanil and placebo responses to give us insight into the importance of placebo-related phenomena as a cause of the response variability as well as an indication of the "true" opioid potency. The placebo response has been incorporated before in pharmacokinetic–pharmacodynamic models of analgesia using both additive and multiplicative approaches (see Luginbühl *et al.*[5], Sheiner *et al.*[24], Mandema and Stanski,[25] and Romberg *et al.*[26] for examples). Currently, we used an additive approach because placebo and alfentanil responses were not correlated (as determined from area under the effect response curves; data not given). The placebo response can be analgesic or hyperalgesic or may contain components of both, but usually, the hyperalgesic response is not acknowledged, and subjects who respond primarily hyperalgesically are considered nonresponders.[22] Our placebo model allows the placebo effect to decrease or increase with time, with different time constants for the increasing (α, equation 5) and decreasing components (β, equation 5) of the placebo response. Our placebo model is similar to one proposed by Mandema and Stanski.[25] The increasing

and decreasing components of their model are additive with respect to baseline; in our model, they are multiplicative (and approximately additive on a log scale), which seems preferable because current cannot be negative. In contrast to what we expected, we did not observe a reduction in the variability of the estimated potency parameter obtained from the combined alfentanil–placebo model in comparison with the alfentanil model. This may be related to the very large analgesic responses after alfentanil relative to placebo (the AC_{50} values indicate that placebo analgesia contributed only 20% to the total analgesic effect) and hence that the major part of the variability was in the opioid and not in placebo-related phenomena.

However, the following caveats should be noted. Although the alfentanil and placebo responses of single subjects were paired, the response of the subject (to alfentanil or placebo) may display large between-day variability. We did not take this into account. Further, the placebo analgesic response is not only related to μ-opioid receptor pathways but also to non–μ-opioid and nonopioid analgesic pathways.[27] These non–μ-opioid pathways may have interacted with the alfentanil response in a more complex fashion than described by our simple additive alfentanil–placebo model.

The absence of observing a significant difference between men and women in the placebo analgesic response is in accord with clinical studies using the post–third molar extraction pain model.[28] These data indicate absence of a sex dependency in the psychological and physiologic aspects of placebo responses, something that intuitively is not expected.[28] Because sex differences in analgesic responses are highly dependent on

Fig. 7. Measured alfentanil plasma concentration *versus* analgesia and sedation. Values reported are population averages. Error bars are omitted for clarity. (*A*) Analgesic effect in responses to pain from transcutaneous electrical stimulation shows a wide clockwise hysteresis loop. (*B*) Analgesic effect in response to thermal pain shows a small anticlockwise hysteresis loop. (*C*) Alfentanil-induced sedation causes a small clockwise hysteresis loop. C_P = plasma concentration; VAS = visual analog scale score.
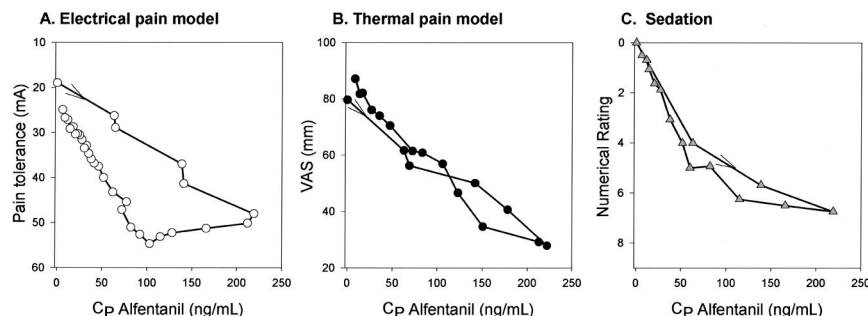
the specific pain model, significant sex differences in placebo responses may be visible in other pain models.

Alfentanil Onset and Offset Times

Alfentanil analgesic onset and offset (*i.e.*, $t_{1/2}k_{e0}$) are determined by multiple factors such as cardiac output, brain blood flow, transport across the blood–brain barrier, diffusion within the brain compartment to relevant μ-opioid receptor sites, receptor association and dissociation kinetics, activation of second messenger systems, and neuronal dynamics. Our estimate of the alfentanil $t_{1/2}k_{e0}$ using TES ($t_{1/2}k_{e0}$ 7–9 min) is large compared with values obtained from studies measuring the effect of alfentanil on the electroencephalogram, pressure pain, and pupil diameter ($t_{1/2}k_{e0}$ approximately 1 min).[29-32] This prompted us to conduct additional experiments using a different pain model (heat pain) and to perform a *post hoc* comparison of the pharmacodynamic parameters obtained from TES and heat pain models. We further performed an analysis on sedation data obtained in our initial study 1 (note that the sedation scoring scales were chosen to allow for the estimation of onset and offset times rather than to allow for an accurate description of the level of sedation). The estimated $t_{1/2}k_{e0}$ values derived from TES differed significantly with the values obtained from heat pain (0.4 min) and sedation (2 min). In contrast, analysis of TES and heat pain data yielded a similar estimate of the analgesic potency of alfentanil (AC_{50} values 130–140 ng/ml; table 2). This indicates that TES and heat pain models are comparable in steady state situations but differ under dynamic conditions. A similar "slow" alfentanil onset was observed previously using electrical stimulation of the finger and toe.[33] The slow TES response is not explained by a slow adaptation or habituation to the electrical stimulation, because no-drug studies showed constant TES response times during a 5-h measurement period in 9 of 10 subjects. Possible mechanisms for the relatively slow alfentanil response to TES include the following: (1) Different pain models may activate different pain pathways with differences in central processing (*e.g.*, due to differences in neuronal dynamics). It is possible that slower neuronal dynamics and activation of short-term potentiation at sites within the central nervous system involved in the processing of electrical pain responses may have caused the longer delay in alfentanil responses with TES, whereas no such slow dynamics were activated with heat pain. (2) A slow component in the TES response may be linked to placebo-related phenomena. Incorporating the placebo response in the alfentanil pharmacokinetic–pharmacodynamic model reduced the value of $t_{1/2}k_{e0}$ by 2 min. Although 7 min is still a relatively large value, this observation suggests that at least part of the slow alfentanil response to TES is linked to placebo-related components. Our model may have been unable to extract the true magnitude of these components and hence may

have overestimated the "true" alfentanil $t_{1/2}k_{e0}$. (3) In most of the heat pain (but not TES) responses, periods of hyperalgesia (*i.e.*, VAS scores > baseline) were observed during the slow decrease in alfentanil blood concentration (fig. 4). Under various circumstances, opioids may cause hyperalgesia due to activation of *N*-methyl-D-aspartate receptors.[34] A (slow) hyperalgesic component arising during heat pain testing (but not during TES) may have canceled out against a slow analgesic component, causing an overall short value of $t_{1/2}k_{e0}$ in the heat pain experiments. In a preliminary analysis, we added a hyperalgesic component in the pharmacokinetic–pharmacodynamic model of VAS analgesia and observed a significant increase in $t_{1/2}k_{e0}$. (4) A combination of items 1, 2, and 3 may have caused the relatively slow alfentanil response to TES. Studies using the technique of functional magnetic resonance imaging may shed further light on the mechanisms of the observed slow onset and offset times of alfentanil observed with electrical pain but not with other surrogate measures of opioid effect (sedation/electroencephalogram, analgesia from heat and pressure pain).[35]

Alfentanil Pharmacokinetics

A discrepancy was found between the target concentrations and the actually measured plasma concentrations related to a much smaller central volume (V_1) in our population than provided by the pharmacokinetic set of Maitre *et al.*[9] This discrepancy may be related to differences in the study population (in contrast to Maitre *et al.*, we studied a homogenous young population), infusion regimen, sample times, and duration of the studies. A three-compartment model described the pharmacokinetic data best, and the model output adequately characterized the observed plasma concentrations in this study (figs. 2 and 4). Neither sex nor age had a significant effect on the estimated pharmacokinetic parameters. This stands in contrast to a study from our institution showing a significant effect of age on alfentanil pharmacokinetic in surgical patients.[36] A possible explanation for the difference may be the small age range and the absence of underlying disease, surgery, and inflammation in the current study.

The goal of the current study was to increase our insight into the pharmacodynamics of potent opioids such as alfentanil, allowing us to optimize perioperative analgesic treatment. Although we believe that it is important to have knowledge on the potency and the onset and offset times of the opioids we administer, these population values will be of limited value when the determinants of variability are unavailable to predict the opioid requirements of individual patients. The current study indicates that sex and placebo-related phenomenon are unable to explain the large between-subject variability in alfentanil analgesic responses. The current absence of a cogent explanation for patient variability

suggests that opioids are still best used by titration against analgesic effect.

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