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Comparison of Five Experimental Pain Tests to Measure Analgesic Effects of Alfentanil

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Background: **Several experimental pain models have been used to measure opioid effects in humans. The aim of the current study was to compare the qualities of five frequently used experimental pain tests to measure opioid effects.**

Methods: **The increase of electrical, heat, and pressure pain tolerance and the decrease of ice-water and ischemic pain perception was determined at baseline and at four different plasma concentrations of alfentanil (n = 7) administered as target controlled infusion or placebo (n = 7). A linear mixed-effects modeling (NONMEM) was performed to detect drug, placebo, and time effect as well as interindividual and intraindividual variation of effect.**

Results: **Only the electrical, ice-water, and pressure pain tests are sensitive to assess a concentration–response curve of alfentanil. At a plasma alfentanil concentration of 100 ng/ml, the increase in pain tolerance compared with baseline was 42.0% for electrical pain, 22.2% for pressure pain, and 21.7% for ice-water pain. The slope of the linear concentration–response curve had an interindividual coefficient of variation of 58.3% in electrical pain, 35.6% in pressure pain, and 60.0% in ice-water pain. The residual error including intraindividual variation at an alfentanil concentration of 100 ng/ml was 19.4% for electrical pain, 6.1% for pressure pain, and 13.0% for ice-water pain. Electrical pain was affected by a significant placebo effect, and pressure pain was affected by a significant time effect.**

Conclusion: **Electrical, pressure, and ice-water pain, but not ischemic and heat pain, provide significant concentration–response curves in the clinically relevant range of 200 ng/ml alfentanil or lower. The power to detect a clinically relevant shift of the curve is similar in the three tests. The appropriate test(s) for pharmacodynamic studies should be chosen according to the investigated drug(s) and the study design.**

EXPERIMENTAL pain models are often used to measure analgesic drug effects and are important tools to compare the analgesic potency of different drugs and to investigate drug interactions.[1,2] Measurements with experimental pain tests may be biased by relevant placebo and time effects. Human studies are often conducted with healthy volunteers to allow for maximally standardized conditions. Experimental pain models to measure analgesic drug effects should therefore be noninvasive, nonnoxious, standardized, and repeatedly applicable.[3] The sensitivity of the test to the drug effect may be reduced by concomitant placebo and time effects as well as by interindividual and intraindividual variability of the end point (*i.e.*, pain tolerance, pain intensity). An ideal pain test to be used for pharmacodynamic research is sensitive enough to provide a reasonable concentration–response curve in the clinical concentration range, with minimal placebo and time effect.

Most of the pharmacodynamic studies on opioids have been performed with parameters derived from electroencephalography as a measure for effect, although opioid-induced electroencephalography changes occur only at drug concentrations above the clinically used range.[4] In contrast, experimental pain models are useful for measuring the opioid effect in a clinically relevant concentration range. The plasma concentration– effect relation has therefore been determined for various opioids administered intravenously, epidurally, or intrathecally in patients[5] and volunteers.[6,7] The technique of intravenous drug administration by target controlled infusion,[8,9] some even with individual tailoring,[6,7] eliminated the instability of study conditions with bolus drug administration. In awake subjects, the analgesic effect of opioids measured with experimental pain paralleled the occurrence of side effects[2,7] with a linear concentration–response curve for alfentanil with a cold pain model in the concentration range of 25–200 ng/ml[2] or lower.[10]

Different types of electrical pain stimulation, pressure, ice-water, and tourniquet effort pain have been used in various studies to investigate analgesic drug effects.[11–15] Only a few of them reported a concentration–response curve.[6,7,16] There are no data available comparing more than three experimental pain models to assess analgesic drug effect with the same drug in the same subjects. Furthermore, there is no concentration–response model including placebo and time effect for experimental pain models available, because most studies including a placebo group were analyzed with analysis of variance or similar statistical methods.

The aim of this randomized, double-blind, placebo-controlled study was to determine the concentration–response curve of alfentanil using two tonic and three phasic pain tests, to compare the opioid sensitivity of these tests, to distinguish drug, placebo, and time effect, and to assess interindividual and intraindividual variability.

Methods

Volunteers

After obtaining approval from the ethics committee of the Medical Faculty of the University of Bern, 14 healthy paid volunteers with a mean age of 24 yr (range, 22–28

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yr) were enrolled, and written informed consent was obtained according to the Helsinki Declaration. Seven individuals (four men, three women) were randomly assigned to the drug group, and the other seven (three men, four women) were assigned to the placebo group. Allergies, any drug therapy, a history of adverse reactions to anesthetics, regular consumption of more than 20 g of alcohol per day,[17] and pregnancy were the exclusion criteria.

Study Plan

The volunteers were asked to abstain from alcohol and excessive coffee consumption (defined as > 5 cups or 400 mg caffeine[18]) for 24 h and from drinking and eating for 6 h before testing. The volunteers rested comfortably in a supine position during the experiments. They were informed that the computer-controlled infusion would contain either an opioid or a placebo (normal saline) and that four different plasma concentrations were targeted in ascending order.

The volunteers were monitored with electrocardiogram, noninvasive blood pressure, and pulse oximetry. The end-expiratory carbon dioxide concentration was measured through a nasal cannula attached to a Hewlett Packard (HP M1025B) anesthetic gas analyzer (Hewlett-Packard Company, Andover, MA). Before pain testing, an intravenous infusion with Ringer's lactate (2 ml · kg^{-1} · h^{-1}) was started. Another intravenous line was inserted on the opposite arm for blood sampling. After a trial testing to familiarize the volunteers with the procedures, six test series were performed: at baseline, at four different target plasma concentrations of alfentanil or placebo (50, 100, 150, and 200 ng/ml in ascending order), and at 60 min after the infusion was stopped (fig. 1). Alfentanil (Rapifen, Janssen Pharmaceutica, Beerse, Belgium) or placebo (normal saline) was delivered with a target controlled infusion in a randomized (drawing lots) double-blind manner (syringes prepared by another person than the investigator). A Harvard 22 infusion pump (Harvard Apparatus, South Natick, MA) was driven by an IBM-compatible laptop with the Stanpump program§ using pharmacokinetic parameters for alfentanil calculated from Raemer *et al.*[8] and k_{e0} from Scott and Stanski.[19] The infusion was started after the baseline test series had been completed.

Electroencephalography data on alfentanil show a $T_{1/2}$ K_{e0} of 1.1 min or lower,[4,20] illustrating the very short time lag between achievement of a certain plasma concentration an the measured effect. There are no data available comparing the time course of electroencephalography and analgesic effects of opioids because the k_{e0} value of opioids has only been determined with electroencephalography. We therefore assumed similar pharmacodynamics of electroencephalography and analgesic

§ Software freely available from the author: S. L. Shafer, M.D., Anesthesiology Service (112A), PAVAMC, 3801 Miranda Avenue, Palo Alto, California 94304.

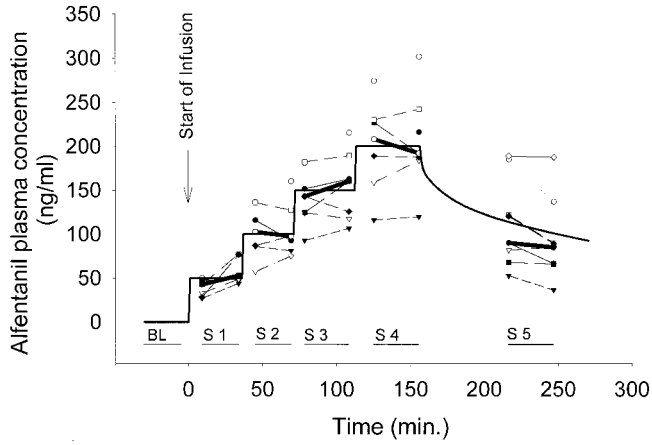

Fig. 1. Study plan and measured alfentanil plasma concentrations. Predicted (thin solid line) and median measured (thick solid lines) alfentanil plasma concentrations in the alfentanil group. Measured alfentanil concentrations of individual subjects (fine interrupted lines with different symbols). The series of pain tests are indicated at the bottom: baseline (BL) and series 1–5 (S 1–5). Reaction time to an acoustic signal and tolerance to ice-water, ischemic, electrical, heat, and pressure pain were assessed in randomized order in each test series.

effect of alfentanil and allowed an equilibration period 10 min before starting the new test series after changing the target concentration. Before and after each test series, a venous blood sample was taken for analysis of the alfentanil plasma concentration. The blood samples were immediately stored at 4°C and centrifuged at 3,500 rpm for 30 min after the last test series. The plasma was frozen at −18°C for later analysis. The alfentanil plasma concentration was determined by high-performance liquid chromatography.[21] The detection limit of the assay was 2 and 0.9 ng/ml at a signal-to-noise ratio of 10:1 and 3:1, respectively. The intraday coefficient of variation (n = 5) was 3.9, 4.5, and 4.9% at alfentanil concentrations of 484.4, 193.8, and 48.4 ng/ml, respectively. The interday coefficient of variation at the same concentrations (n = 15) was 4.5, 5.8, and 6.1%, respectively.

Experimental Pain Tests

Pain threshold can also be increased by pure hypnotic drugs.[22,23] Pain tolerance, in contrast, is more reliable in detecting true analgesic effects.[24] Experimental pain threshold is less increased by opioids than pain tolerance.[25] We therefore chose pain tolerance as an end point for the measurement of drug effect with variable stimulation intensity in the phasic pain tests.

The same investigator always performed the pain tests. The participants received a standardized oral and written instruction on the tests and on the definition of pain tolerance.

Electrical Pain Test. A 1-mm-diameter pin electrode[26] was attached to the second or third toe of the dominant foot after superficial scratching of the stratum corneum with a scalpel. Correct electrode positioning was assumed when current intensities less than 0.8 mA

elicited a distinct pinprick pain. A 25-Hz train of 0.5-ms constant-current square-wave pulses of increasing intensity (each 0.01 mA higher than the preceding stimulus) was delivered from a computer-controlled constant current stimulator (manufactured by the Center for Sensori-Motor Interaction, University of Aalborg, Denmark). The volunteer interrupted the stimulus by pressing a button when he/she did not want the intensity to be further increased (pain tolerance = maximal current tolerated; cutoff limit, 10 mA). The mean of three determinations was recorded in each test series.

Pressure Pain Test. An electronic pressure algometer (Somedic AB, Stockholm, Sweden)[11,23] was used to determine the maximally tolerated pressure on the pulpa of the third and fourth finger of the dominant hand. A probe with a surface area of 0.28 cm^2 was used, and the pressure was increased at 30 kPa/s. The volunteer pressed a button when he/she did not want the pressure to be further increased (pressure pain tolerance; cutoff limit, 1,500 kPa).

Heat Pain Test. A computerized version of the Thermotest (Somedic AB)[27] was used to determine the maximally tolerated temperature on the volar side of either forearm. Starting at a baseline temperature of 30°C, the thermode was heated at a rate of 2.0°C/s. The volunteer pressed a button when he/she did not want the temperature to be further increased (pain tolerance = maximal temperature tolerated; cutoff limit, 52°C). This started the thermode to cool to baseline temperature.

Ice-Water Pain Test. The dominant hand was immersed in ice water (1.5 ± 0.5°C) for a maximum of 120 s.[28] The perceived pain was continuously registered with an electronic visual analog scale (0 = no pain, 10 = maximal and intolerable pain). The area under the visual analog scale–time curve was used as end point for pain intensity.

Ischemic Pain Test. A maximal-effort tourniquet test was performed on the nondominant arm.[29] After compression of a power grip hand exerciser calibrated at 25 pounds (Smith & Nephew Inc., Emmenbrücke, Switzerland) at the individual subject's maximal rate for 120 s, a blood pressure cuff was inflated to 250 or 100 mmHg above systolic pressure, whichever was the higher. With inflation of the cuff, the continuous registration of the perceived pain with an electronic visual analog scale was started. The area under the visual analog scale–time curve was used as an end point for pain intensity, as with ice-water pain.

Reaction Time. The average reaction time to five consecutive 1,000-Hz tones delivered from a computer with randomized intervals of 3–8 s was also determined.

Data Analysis and Statistics

Performance of the Target Controlled Alfentanil Infusion. The prediction error of the pharmacokinetic model was calculated from each of the measured plasma concentrations (10 samples per subject, equation 1).

$$PE = [(Cm - Cp)/Cp] \times 100 \quad (1)$$

where Cm represents the measured concentration and Cp the predicted concentration. The median prediction error (measuring the bias) as well as the median absolute prediction error (measuring the accuracy) from the 10 measured concentrations were computed for each individual.[30] Subsequently, the mean (SE) of the median prediction error and the mean (SE) of the median absolute prediction error were calculated.

Linear Regression Analysis of Alfentanil, Placebo, and Time Effect. In a first step, a linear model relating the effect to a baseline effect, the measured alfentanil concentration, the placebo effect, and the time effect, was defined (equation 2).

$$E(t) = E_0 + k_a \times Cp + k_p \times Cpl + k_t \times t \quad (2)$$

where E(t) is the measured effect at time t, E_0 is the baseline effect, Cp is the average of the measured alfentanil concentrations before and after the test series, Cpl is the assumed placebo concentration (arbitrarily set equal to the target plasma concentration chosen for alfentanil for the test series 1 to 4, and to 100 for the last test series during decay), t is the time, and k_a, k_p, and k_t are the respective slope parameters.

The interindividual variability of the estimated parameters (E_0 and slope parameters) was modeled with an additive error model:

$$P_i = P_{TV} + \eta_i \quad (3)$$

where P_i denotes the parameter of the i^{th} individual, P_{TV} is the typical parameter value of the population, and η_i is the random interindividual variability of the parameter (with mean 0 and variance ω^2).

The residual error of the predicted effect including intraindividual variation[31] was assumed to be additive as well:

$$E_{ij} = E_{TVi} + \varepsilon_{ij} \quad (4)$$

where E_{ij} denotes the effect in the i^{th} individual at the j^{th} measurement, E_{TVi} is the typical effect value of the i^{th} individual, and ε_j is the residual variability of the effect at the j^{th} measurement (with mean 0 and variance σ^2).

This linear mixed-effects model was implemented in Fortran pseudocode for use with the nonlinear mixed-effects modeling program NONMEM.[32] The NONMEM objective function was minus twice the logarithm of the likelihood. The objective function was minimized to obtain the best estimation of the model parameters. By setting one of the slope parameters to zero, a reduced model was obtained. The significance of each of the parameters was tested with the likelihood ratio test. A difference of the minimal value of the objective function between the reduced and the full model exceeding

3.841 was considered significant ($P < 0.05$). If NONMEM aborted the covariance step and SEs were therefore not obtainable, if the 95% confidence interval of a slope parameter included zero or if the difference between the full and the reduced model was not significant, the parameter was removed from the model. Thus, the final model to predict the drug effect was obtained by a stepwise elimination of nonsignificant parameters from the full model.

Results

Pain Tests and Side Effects

The six pain test series were successfully performed in all the 14 subjects. In one subject in the alfentanil group, the tolerated current in the electrical pain test was twice to three times as high as in the remainder of the study population. After the experiments, he reported that the pain sensation temporarily decreased after an initial increase and that it later increased again until it became intolerable. Because all the other volunteers reported an almost linear increase of pain, a technical problem with the stimulator could not be excluded, and the data of the electrical pain test in this subject were excluded from the analysis. Reaction time was not significantly affected by alfentanil and hence was not the reason for the increases in pain tolerance thresholds.

In the alfentanil group, two subjects complained of itching on the upper body, two experienced nausea, and one vomited at the highest plasma concentration. An increase of the end-tidal carbon dioxide concentration from a mean (SD) of 5.4 (0.3) to 6.4 (0.4) vol% was observed in the alfentanil group (paired *t* test, $P = 0.004$). The increase of the end-tidal carbon dioxide in the placebo group was smaller but also significant (from 5.3 [0.3] to 5.7 [0.4] vol%; $P = 0.002$). There were no other side effects in the placebo group. Blinding of the investigators could thus not be maintained because of the side effects. There were no side effects from the pain tests themselves.

Performance of the Computer-controlled Alfentanil Infusion

The measured alfentanil plasma concentration data were plotted together with the target concentrations (fig. 1). The bias (mean [SE] of the median prediction error) was −3.91% (SE, 1.55) and the inaccuracy (mean [SE] of the median absolute prediction error) was 10.04% (SE, 1.19). This demonstrates that the performance of the selected pharmacokinetic parameters to predict plasma concentrations in our study population was comparable to the results of a previous study.[8] Because the absolute prediction error in two subjects was substantial (fig. 1), the measured effect was related to the measured and not to the predicted alfentanil concentrations.

Linear Regression Analysis

The raw data together with the final model of the population and the *post hoc* Bayesien predictions for each individual are plotted in figure 2. Table 1 shows the final models obtained from linear mixed-effects modeling with NONMEM. In the electrical and ice-water pain tests, NONMEM did not report SEs of the parameter estimates for the complete model because of numerical difficulties with overparametrization. Therefore, the model was reduced in a stepwise manner by one parameter until a complete NONMEM run could be performed. The models with a complete NONMEM run including the estimation of SEs were compared with the objective function as described.

The slope parameter, k_a, was significant for electrical, pressure, and ice-water pain but not for the ischemic and heat pain models, *i.e.*, the alfentanil concentration did not significantly influence the measured effect in these two pain models. A placebo effect was observed in the electrical and the ischemic pain models, and a time effect was observed in the pressure pain model. With the final model, the alfentanil effect independent of placebo or time effect (in percent of the baseline effect) of 100 ng/ml plasma concentration was 42.0% for electrical pain, 22.2% for pressure pain, and 21.7% for ice-water pain. The interindividual variability of the slope parameter k_a (alfentanil) expressed as coefficient of variation within the population was 58.3% for electrical pain, 35.6% for pressure pain, and 60.0% for ice-water pain. The residual error of the predicted effect caused by intraindividual variability of pain tolerance, instability of drug concentrations, and sample analysis error is expressed as coefficient of variation of the effect related to the predicted effect an alfentanil concentration of 100 ng/ml ($= (\sqrt{\sigma^2}/E_{100}) \times 100$). The residual error was 19.4% for electrical pain, 6.1% for pressure pain, and 13.0% for ice-water pain (table 1).

Discussion

In the current study we described concentration–response curves of alfentanil for electrical pain, ice-water pain, and pressure pain tests. It was not possible to detect a significant drug effect on ischemic pain and heat pain within the investigated alfentanil concentration range of 50–200 ng/ml.

As in another study,[7] the data were best described with a linear response curve. The maximal-tolerated stimulus intensity at the highest alfentanil target concentration was already close to the cutoff limit in two subjects in heat pain and one subject in pressure pain.

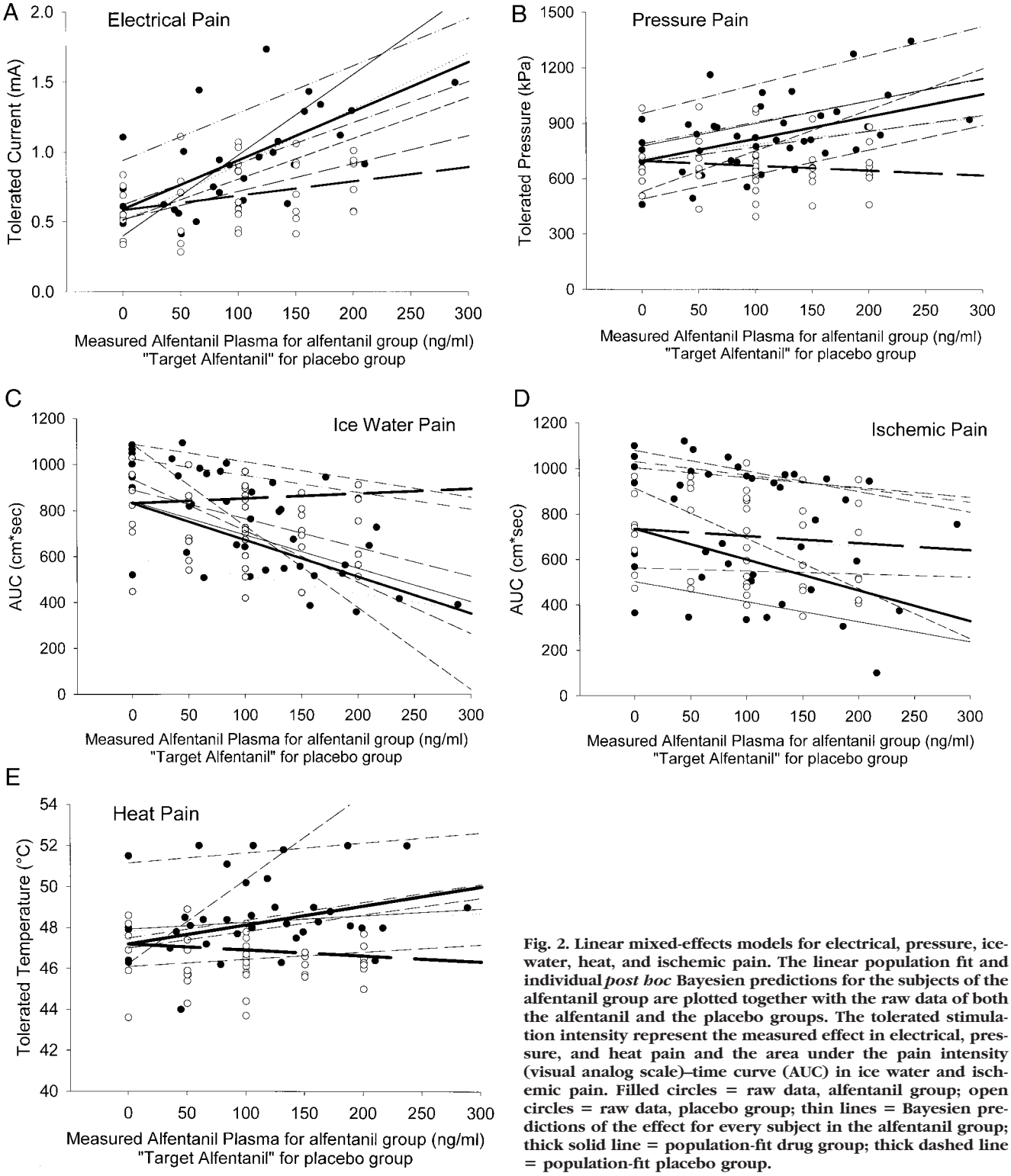

Fig. 2. Linear mixed-effects models for electrical, pressure, ice-water, heat, and ischemic pain. The linear population fit and individual *post hoc* Bayesien predictions for the subjects of the alfentanil group are plotted together with the raw data of both the alfentanil and the placebo groups. The tolerated stimulation intensity represent the measured effect in electrical, pressure, and heat pain and the area under the pain intensity (visual analog scale)–time curve (AUC) in ice water and ischemic pain. Filled circles = raw data, alfentanil group; open circles = raw data, placebo group; thin lines = Bayesien predictions of the effect for every subject in the alfentanil group; thick solid line = population-fit drug group; thick dashed line = population-fit placebo group.

Our results with the electrical, ice-water, and pressure pain tests are in concordance with previous data[2,10,16,22,33–39] where these pain tests have been successfully used to define concentration–response curves.

In most studies, drug effect data were analyzed with repeated-measures analysis of variance on ranks or with similar methods. These methods cannot distinguish between interindividual and intraindividual variability of the drug effect, which may be important for interpretation of results. With the mixed-effects model, it was also possible to determine concentration–effect curves for each individual, based on the informa-

Table 1. Results of Linear Mixed-Effects Modeling of Five Experimental Pain Tests: The Final Models

Pain Test		E_0	K_a	K_p	K_t	$\sqrt{\sigma^2}$	−2LL
Electrical pain	Parameter estimates	0.59 mA	0.00248	0.00103	NS	0.192 mA	−166.035
	SE	0.067	0.00089	0.00038			
	CV	0.322	0.583	0.002			
Pressure pain	Parameter estimates	696 kPa	1.52	NS	−0.259	51.49 kPa	812.191
	SE	42.1 kPa	0.309		0.109		
	CV	0.251	0.356		−0.91368		
Ice water pain	Parameter estimates	833 cm × s	−1.81	NS	NS	85.08 cm × s	887.981
	SE	53.1 cm × s	0.536				
	CV	0.235	−0.600				
Heat pain	Parameter estimates	47.2°C	NS	NS	NS	0.346°C	103.866
	SE	0.438°C					
	CV	0.025					
Ischemic pain	Parameter estimates	740 cm × s	NS	−0.813	NS	102.47 cm × s	991.958
	SE	74.8 cm × s		0.254			
	CV	0.372		−0.890			

The baseline effect equals the maximal tolerated stimulus intensity at baseline for electrical, pressure and heat pain, and the area under the VAS-time curve for ice water and ischemic pain.

E_0 = baseline effect when no drug is present in the linear model; K_a = slope parameter alfentanil; K_p = slope parameter placebo; K_t = slope parameter time; $\sqrt{\sigma^2}$ = SD of the effect in an individual subject (residual and intra-individual error); −2LL = minimum value of nonlinear mixed-effects model objective function according to the likelihood ratio test; SE = standard error of the parameter estimate; CV = coefficient of variation of the parameter estimate in the study population; NS = not significant.

tion from the whole population and the individual's sparse data.

The concentration–response curve was steeper with the electrical pain test than with the other tests. Whereas the end point of previous studies[16,33] was pain intensity at different drug concentrations elicited by a constant maximal stimulation intensity, our end point was the increase in tolerated stimulation intensity eliciting a constant maximal pain perception. At a plasma alfentanil concentration of 200 ng/ml, our volunteers tolerated a more than twofold increase of the stimulation intensity compared with baseline, which was always below the cutoff limit of 10 mA, where tissue damage might occur. This is in contrast to the pressure pain test, where the tolerated increase in stimulation intensity at the same concentration was only by a factor of 0.5 compared with baseline, and some of the subjects were even close to the cutoff limit of 1,500 kPa.

Only with the ice-water test did we not detect a significant time and placebo effect. The interindividual variability of the slope parameter was equal to that of the electrical pain test and almost double as high as in the pressure pain test.

In the pressure pain test, a significant negative time effect was observed. This decreased the measured absolute effect. Presumably this is a result of sensitization of the tissue in the repeatedly stimulated area. If the time effect on this test is ignored in the analysis of data from a prolonged experimental pain session with a large number of stimulations, its use is limited because the true drug effect will be underestimated. The advantage of the pressure pain test is its smaller interindividual and intraindividual variation of baseline effect and alfentanil slope coefficient.

In the heat pain test, we possibly did not detect an alfentanil effect because the stimulation was performed with a rapid temperature increase of 2°C/s. A rapid temperature increase, exceeding 0.9°C/s stimulates predominantly Aδ-fibers, which are not much affected by opioids.[40] The negative result also fits with previous results on laser-induced heat stimulation in humans.[41]

The lack of alfentanil effect on ischemic pain is similar to previous data on short ischemic pain[29,42] and is also consistent with the low efficacy of opioids to treat intraoperative tourniquet pain.[43] Only with longer-lasting ischemic stimulation has a significant analgesic effect of morphine been observed.[14]

The analgesic profile of alfentanil determined by these experimental pain tests is different from the profile determined for nitrous oxide and xenon.[44] In contrast to alfentanil, nitrous oxide and xenon have a significant analgesic effect on ischemic but not on ice-water pain, whereas the effect on electrical and pressure pain tests were similar.[44] The different experimental pain profiles of alfentanil and nitrous oxide or xenon illustrate the benefit of a multimodel stimulation and assessment technique if the efficacy of a new analgesic drug is to be investigated.

The different slope parameters of the alfentanil concentration–response curves (k_a, equation 2) in the population model was illustrated by the larger alfentanil effect (in percent of baseline) in electrical pain compared with pressure and ice-water pain. This might imply a different power of these tests to detect an analgesic effect of alfentanil or to detect a shift of the concentration–response curve induced by some hypothetical intervention (*e.g.*, administration of another drug, comparison of opioid-naive and opioid-treated subjects). We

tested this by generating 1,000 simulated data sets (studies) based on the data and the NONMEM results with the estimated random effects (for the interindividual and the intraindividual variability) from our study with and without a shift of the dose–response curve. We then tested the hypothesis that NONMEM would be sensitive enough to detect the simulated left shift of 100 ng/ml in the concentration–response curve. This hypothesis was true 774 times in the electrical pain test, 777 times in the ice-water pain test, and 590 times in the pressure pain test. This result suggests that the power to detect a clinically relevant shift of the concentration–response curve is similar for all three tests (*i.e.*, 0.774, 0.777, and 0.590, respectively). Apparently, the power of detecting a shift in the dose–response curve is independent of the steepness of the concentration–response curve.

Coda *et al.*[16,33] reported a time to peak analgesic effect for alfentanil of 15 min with cutaneous electrical pain, which might suggest that our equilibration period of 10 min was too short. Electroencephalography data on alfentanil show a $T_{1/2}$ K_{e0} of 1.1 min or lower,[4,20] illustrating the very short time delay between the time course of plasma concentration and effect-site concentration. We simulated the time course of plasma and effect-site concentrations in our study based on the pharmacokinetic and dynamic parameters used.[8,19] According to this simulation of ascending plasma concentrations (50, 100, 150, and 200 ng/ml), the predicted effect-site concentration reached 95% of the predicted plasma concentration 4.0, 3.0, 2.5, and 2.1 min after the four increasing steps of the plasma target concentration, respectively. Because there are no data available comparing the time course of electroencephalography effects and analgesic effects of opioids, and based on these electroencephalography data, we considered a 10-min equilibration period sufficient. Moreover, the order of stimulation was randomized so that the potential bias would be similar in all pain tests, and only one fifth of the stimuli were performed in the time window between 10 and 15 min after a change in the plasma target concentration.

In conclusion, electrical, pressure, and ice-water pain, but not ischemic and heat pain, provide significant concentration–response curves in the clinically relevant range of 50–200 ng/ml alfentanil. The power to detect a clinically relevant shift of the concentration–response curve is similar for the three tests. Therefore, no single best experimental pain test can be recommended, but the appropriate test(s) for pharmacodynamic studies must be chosen according to the investigated drug(s) and the study design.

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