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The effect of repeated intramuscular alfentanil injections on experimental pain and abuse liability indices in healthy males

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Abstract

Objective—Opioid-induced hyperalgesia (OIH), increased sensitivity to noxious stimuli following repeated opioid exposures, has been demonstrated in pre-clinical studies. However, there is no accepted, prospective model of OIH following repeated opioid exposures currently available in humans. This study assessed a potential prospective OIH model.

Methods—Double-blind intramuscular (IM) injections of a short-acting opioid, (alfentanil 15 mcg/kg; N=8) were compared to active placebo (diphenhydramine 25 mg; N=3) on cold and pressure pain testing and standard abuse liability measures in eight 10-hour sessions (1 injection/session) over 4–5 weeks in healthy pain-free males. Decreases from session baseline pain threshold (PThr) and tolerance (PTol) were calculated to represent hyperalgesia, and were assessed both within and across sessions.

Results—Mean decreases in cold PTol were seen in the alfentanil group at 180 minutes (−3.8 seconds, +/−26.5) and 480 minutes (−1.63 seconds, +/−31.5) after drug administration. There was a trend for differences between conditions on cold PThr hyperalgesia but not for pressure PThr. Alfentanil participants had greater mean ratings on LIKING and HIGH visual analog scales at peak effects (30 minutes), but these scores did not change across sessions.

Discussion—Repeated alfentanil exposures over 4–5 weeks resulted in within session decreases in cold pain tolerance from baseline but these differences were not substantially different from diphenhydramine controls. The results did not support the phenomenon of OIH in this model, although definitive conclusions regarding the existence of OIH in humans likely requires a larger sample size or an alternative model.

Keywords

cold pressor; alfentanil; abuse liability; opioid-induced hyperalgesia; algometer

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DISCLOSURES

The authors have no conflicts of interest relevant to this manuscript to disclose. Preliminary analyses in this manuscript were presented at the 2010 American Pain Society and 2011 College on Problems of Drug Dependence annual meetings.

INTRODUCTION

Prescription opioid medications are increasingly used for moderate to severe chronic noncancer pain. Chronic opioid use, though, is associated with risks of physical dependence and addiction. Hyperalgesia, defined as increased pain sensitivity without a new injury or exacerbation of an old injury, [1, 2], is considered by many clinicians a side effect of chronic opioid use. This pain sensitivity can be diffuse, of a different quality from a patient's chronic pain syndrome, and unassociated with previous tissue damage. However, hyperalgesia is not consistently seen in patients on chronic opioids; no clear temporal relation between the start of opioids and the development of hyperalgesia has been established; and no clear dose effect has been demonstrated. Therefore, the existence of opioid-induced hyperalgesia (OIH) as a clinically meaningful phenomenon is still under considerable debate.

OIH has been well characterized in controlled, pre-clinical studies [3–6]. In pre-clinical models, administration of opioids initially produces an anti-nociceptive effect but then leads to a sustained pro-nociceptive (hyperalgesic) effect after repeated dosing. This biphasic response varies by experimental pain type (e.g., thermal, mechanical, electrical, or chemical) but occurs across a wide variety of opioids [7, 8]. These pre-clinical methodologies are difficult to replicate in humans given ethical and practical concerns of administering opioids chronically to volunteers – potentially inducing physical dependence or contributing to the development of addiction.

Evidence of OIH in humans, therefore, has come mainly from two clinical populations exposed to experimental pain testing: patients with opioid addiction and patients receiving opioids for chronic pain. Cross-sectional studies have shown lower pain tolerance to the cold pressor test (CPT) in opioid maintained former addicted individuals as compared to non-opioid maintained former addicted individuals and compared to healthy controls [9–12]. A similar study showed persons maintained on opioids due to chronic pain (without a history of addiction) have decreased tolerance for experimental pain as compared to persons with chronic pain and not on opioids, as well as compared to healthy controls [13]. However, these cross-sectional studies cannot demonstrate temporality or causality of opioid use and between group differences on pain testing (i.e., hyperalgesia); persons with increased pain sensitivity may be predisposed to developing addiction [14] or persons with opioid addiction may develop increased pain sensitivity after chronic opioid use.

The most consistent evidence for OIH in humans comes from studies in healthy volunteers after a *single* opioid exposure to extremely short acting opioid receptor agonists [15–17]. Double-blind, placebo controlled crossover studies have shown remifentanil infusions can increase areas of secondary hyperalgesia as compared to placebo, and a decreased tolerance to mechanical and heat pain after withdrawal of remifentanil. However, the mechanisms for hyperalgesia after one opioid dose are most likely different from the neural plasticity thought to be the cause of OIH after repeated dosing.

Development of a repeated opioid exposure model of OIH in humans would provide valuable evidence for or against the theory that chronic opioid use changes pain sensitivity. It would avoid the limitations of prior experiments, (e.g., one acute opioid exposure and cross-sectional comparisons). However, this model development is extremely challenging due to potential safety issues, including the risk of establishing opioid dependence and/or increasing subsequent abuse risk. The present study investigated the safety and feasibility of a repeated exposure model of OIH as an initial step in model development. If validated, this model could provide evidence in favor of OIH and could be a new tool to screen opioid medications for their OIH effects. Additionally, this model could be used to understand the pathophysiology underlying OIH.

Therefore, the specific aims of the current study were to: 1) determine the within and between session changes in experimental pain testing parameters after intramuscular (IM) administration of the short-acting mu opioid receptor agonist alfentanil; and 2) report on the safety and abuse liability parameters associated with this model. It was hypothesized that repeated opioid exposures would lead to significantly decreased pain threshold and tolerance relative to active placebo exposure.

MATERIALS AND METHODS

Participants

The study was approved by the Institutional Review Board at Johns Hopkins University, conducted in accordance with the Declaration of Helsinki, and registered at www.clinicaltrials.gov (NCT00991809). Participants provided written informed consent before engaging in study activities.

Twenty-two healthy males ages 18–55, with body mass index of 20–30, and without a history of chronic pain, clinically significant psychiatric illness or lifetime history of a substance use disorder (except nicotine dependence or alcohol abuse/dependence in remission) were recruited (Figure 1). Given the exploratory nature of this study, females were excluded to eliminate heterogeneity of pain responses associated with different menstrual phases [18–20], with the expectation that females would be studied after safety and feasibility were established. Persons could also be excluded for the use of opioids in the last 3 months, current illicit drug use, self-report of acute pain at screening, neurologic or psychiatric condition known to influence cold pressor testing, current use of prescribed or over the counter pain medications, previous adverse reactions to the study medications, an ability to withstand the full 5 minutes of cold pressor testing, an inability to tolerate repeated pain testing, or an inability to commit to the schedule of experimental sessions. Participants who used illicit substances during the trial were withdrawn from further participation. If a participant arrived with a positive blood alcohol level (BAL) on breathalyzer, the session was either delayed until the BAL reached 0 or the session was rescheduled. One session was started with a positive BAL, and those results were removed from analysis given the analgesic effects associated with ethanol [21, 22].

Participants were initially screened over the phone and then scheduled for an in-person screening visit. Each person underwent a comprehensive medical history and physical exam, including electrocardiogram; personality testing (NEO-PI [23]); a screening for psychological distress (SCL-90 [24]); urine drug screen; breathalyzer; and an exposure to the pain testing procedures. A board-certified psychiatrist (DAT) performed a comprehensive psychiatric exam to determine presence of significant psychiatric illness if the SCL-90 was abnormal. Participants who met inclusion and exclusion criteria were scheduled for the first experimental pain session. Participants were told to avoid pain medications before each day of pain testing and were not allowed caffeine or nicotine during sessions.

Experimental Design

This was a randomized, double-blind placebo controlled mixed within- and between-group study design. Within-subject variables included session number and time since IM injection while the main outcome of interest involved analysis of the between-group variable, experimental medication received. Participants were randomized to ensure a 2:1 ratio of alfentanil to diphenhydramine completers. There were 8 experimental pain testing sessions, separated by 3–4 day washout period. On session days, participants arrived at the test site at 8AM. A physician was available for 4 hours after each IM injection. Session rooms were maintained at a constant temperature and pain testing began and ended at the same time each

day (unless the participant arrived with a positive BAL) to control for circadian rhythm effects on pain. Female research assistants administered all pain testing sessions, with the same assistant for each session maximized. Participants were compensated for their participation, including a completion bonus after the eighth session.

Procedures

Study Medication—Alfentanil was selected as the opioid agonist for its short onset of action, relatively short half-life, and favorable safety profile in previous IM experiments with healthy volunteers [25–27]. 15 mcg/kg was the dose chosen as it has been demonstrated to produce analgesia in clinical settings [26, 27].

An active placebo was used to enhance blinding of drug conditions. Diphenhydramine was chosen as the active placebo for its similar cognitive side effects as compared with mu opioid receptor agonists in order to prevent expectancy bias, its known low abuse liability [28], and its previous use as an active placebo in experimental pain testing [29–31]. Alfentanil and diphenhydramine were prepared using commercially available drugs (alfentanil 500 mcg/mL- Hospira, Lake Forest, IL; diphenhydramine hydrochloride 50 mg/mL- Baxter Healthcare Corp., Deerfield, IL). A total volume of 4 mL per IM injection was prepared using bacteriostatic saline to dilute study drugs. Nurses administered the IM injection in the quadriceps, alternating sides for successive sessions.

Pain Assessments—At baseline, as well as 30, 90, 180, 270, 360 and 480 minutes after IM injection, assessments of pain and abuse liability were performed in the following order: measurement of pupil diameter, subjective and objective measurements of drug effect, vital signs, algometer for pressure pain, and cold pressor testing. A minimum of 60 seconds between each type of pain test was used to minimize habituation effects. Participants closed their eyes or looked away during each pain assessment. All data were collected on a Macintosh computer and entered by the research assistant or participant.

Cold pressor pain was assessed by having the participants immerse their dominant hand up to the wrist in 4°C water [32]. The water temperature was maintained (+0.1°C) by a refrigeration unit (Fisher Scientific Co., Suwanee, GA); water was constantly circulated to prevent local warming around the submerged hand. Participants were instructed to keep their hand submerged until “the pain became intolerable.” Cold pain threshold was indexed as the time from hand immersion until the participant first noticed pain, and tolerance was the time from immersion until the participant removed the hand from the water. Submersion was discontinued after 5 minutes for safety. Time was recorded on the session computer by having the research assistant click on a start button when the hand was entered and a stop button when hand was withdrawn from the water.

Pressure pain threshold was assessed using a standard algometer with a 1-cm^2 probe (JTECH Medical, Salt Lake City, UT) [33, 34]. Pressure pain threshold was assessed twice on the non-dominant trapezius muscle on bare skin, and the average of these measurements was calculated as the pressure pain threshold index. Briefly, the examiner applied pressure, at a constant rate (30kPa/second) and participants were instructed to immediately inform the examiner when the pressure first felt painful. The examiner recorded the pressure (kPa) at which stimulation was discontinued.

Subjective and Observer-Rated Opioid Effects—Subjective effects assessments consisted of visual analog scales (VAS) as well as a 37-item participant-rated adjective rating questionnaire[35, 36]. These are standard measures of opioid abuse liability in healthy volunteers. [37–39] There were six VASs: HIGH, DRUG EFFECTS, GOOD EFFECTS, BAD EFFECTS, LIKING, and SICK. Each VAS was a horizontal line on the computer screen,

and the participant positioned an intersecting vertical line using the mouse to indicate the score. The ends of the horizontal line were labeled “None (0)” and “Extremely (100)”, and responses were scored proportionately on a 100-point scale. The adjective rating questionnaire consisted of items that the participant rated on a five-point scale from 0 (not at all) to 4 (extremely); the items constituted two scales: a 16-item opioid agonist subscale (adjectives associated with morphine-like effects), and a 21-item withdrawal subscale (adjectives associated with opioid withdrawal-like effects). Item ratings were summed to produce total scores for the subscales. If appropriate, baseline measurements were obtained for scales (i.e., not for scales that explicitly asked participants to describe the effect of the drug, as no drug had been yet administered) and repeated at the same time points as pain assessments.

Observer ratings were done using the same adjective rating scale at the same time as the subjective adjective scale. Ratings were made by a trained research assistant, blinded to drug administered. Each rater was familiar with recognizing acute drug effects and was present throughout the session.

Physiological Measures—Heart rate, blood pressure, skin temperature, respiratory rate, and oxygen saturation were monitored throughout each session. These measures were collected at baseline, and before and after cold pressor testing using a Criticare Non-Invasive Patient Monitor (model 507S, Criticare Systems, Inc., Waukesha, MI). The blood pressure cuff was placed on the participant’s non-dominant arm (not involved in cold pressor testing). Skin temperature was monitored using a skin surface thermistor taped to the ring finger of the hand not involved in cold pressor testing, and the oxygen saturation clip was placed on the middle finger of the same hand. Pupil diameter was assessed with a digital pupilometer (Neuroptics, Inc., Irvine, CA) in constant room lighting.

Plasma Analysis of Alfentanil Concentrations—On sessions 1, 4, and 8, nursing staff inserted an IV catheter for blood collection in the non-dominant arm (not used for cold pressor testing). Blood draws occurred at baseline and 15, 30, 45, 60, 90, 120, 240, and 480 minutes after the IM injection. Samples for alfentanil testing were frozen at −80°C until analysis. Liquid chromatography with tandem mass spectrometry was used to measure drug concentration and performed at the National Institute on Aging Intramural Research Program in Baltimore, MD. The quantification of alfentanil was accomplished using area ratios calculated using loperamide as the internal standard, where the concentration of the internal standard was set at 25 ng/ml. Calibration standards were prepared daily and were 100 ng/ml, 50 ng/ml, 25 ng/ml, 12.5 ng/ml, 6.25 ng/ml, 3.125 ng/ml, and 1.562 ng/ml.

Statistical Analysis

The primary outcome variables were the changes over time on measures of (1) cold pain threshold, (2) tolerance, and (3) pressure pain threshold. Within session increases from baseline threshold and tolerance on pain testing represented analgesia provided by the drug; decreases from baseline represented hyperalgesia. Descriptive analyses only were performed on the data, as the sample size (N=11) was too small for repeated measures multivariable analysis. However, online supplemental material includes outcomes from exploratory multivariable analyses.

RESULTS

Participants

42 participants provided consent and were screened; 22 were randomized, 10 to receive diphenhydramine and 12 to alfentanil; and 11 completers were included in the analyses

(Figure 1). There were differences between those who were and were not analyzed. Those analyzed reported a higher mean number of alcohol beverages consumed per week, and were more likely to report a past use of illicit substances (Table 1). Additionally, two persons were not analyzed (both in the diphenhydramine condition) due to an ability to withstand the cold pressor test for 300 seconds, thus those not analyzed had a higher baseline mean threshold for pressure and cold pain and higher mean cold pain tolerance.

Looking at those analyzed, the diphenhydramine completers (N=3) were older, all African American, and had a higher mean baseline pressure pain threshold but a lower mean baseline cold pain threshold and tolerance. Individual demographic and personality differences (e.g., neuroticism) may have contributed to the differences in pain testing[40–1], but the small sample size did not allow for testing of these hypotheses.

Pain Testing

Primary Outcomes

Cold pain hyperalgesia: Hyperalgesia was hypothesized to occur both within each session, manifested as a decrease from session baseline on pain threshold and/or tolerance outcomes, as well as across sessions, manifested as a trend for larger decreases from session baseline on these outcomes across successive sessions. There were between group differences in baseline measures (i.e., before any drug exposure in Session 1) of cold pain tolerance (PTol) but not threshold (Table 1). Analgesia associated with alfentanil was observed at 30 and 90 minutes (Figure 2), but no comparable analgesia (>5 seconds increase from baseline cold PTol) was seen with diphenhydramine. As hypothesized, mean decreases from session baseline cold PTol were seen in each session (Figure 3), usually towards the end of the session. There were no identifiable trends to indicate that increasing number of exposures to alfentanil had any effect on hyperalgesia.

Further evidence against hyperalgesia was provided by analysis of baseline pain testing. As can be seen in Figure 4, neither condition showed a decrease in baseline cold pain tolerance across the 8 sessions. Similarly, baseline cold pain threshold did not decrease across sessions; rather there was a trend for an average of 0.7-second increase with each session. This most likely represents habituation to the cold pressor test.

Pressure pain (algometer) hyperalgesia: There was a difference in baseline (session 1 before any drug administration) pressure pain threshold, with the diphenhydramine group having a higher pain threshold than the alfentanil group: 339 kPa vs. 295 kPa. Although there was a mean decrease in algometer pain threshold from baseline for the alfentanil group at each time point after 30 minutes, this decrease was small and was less than the mean diphenhydramine decreases (Table 2).

Secondary Outcomes

Cold pain analgesia: Consistent with past trials, cold pressor testing was an effective model for opioid analgesia. When examining change from baseline (CFBL) PTol using pooled data from all sessions, there was greater tolerance of cold pain by alfentanil versus diphenhydramine groups at 30 and 90 minutes post drug administration (Figure 2). The peak increase in cold pressor PTol from baseline provided by alfentanil appeared to increase across sessions 1–6 but then leveled off in sessions 7–8 (Figure 3). This trend provided some evidence for the development of tolerance to the analgesic effects of alfentanil during study participation.

Pressure pain analgesia: At the 30-minute time point, alfentanil was associated with a mean 6 kPa increase from session baseline in algometer PThr while diphenhydramine was associated with a 29 kPa decrease (Table 2).

Subjective and Observer-Rated Opioid Effects

Visual Analog Scales (VAS)—As has been demonstrated in a comparison of inactive placebo to parenteral alfentanil [42], there were differences on mean VAS ratings of LIKING in this experiment between alfentanil and diphenhydramine groups (Table 2). However, there were no increases in these abuse liability measures across the 8 IM injections of alfentanil relative to diphenhydramine. Figure 5 shows mean VAS ratings associated with abuse liability at 30 minutes post drug administration (expected peak drug effects) for each of the 8 sessions. Although total mean scores were higher for alfentanil than diphenhydramine, alfentanil's total scores remained stable while the diphenhydramine scores increased across sessions.

Opioid Adjectives Rating Scales—At all time points, there were higher mean subjective adjective agonist subscale scores for the alfentanil versus the diphenhydramine group (Table 2). There were no differences between conditions for the subjective adjective withdrawal subscale scores, and no withdrawal from alfentanil appeared to occur as both the subjective and objective withdrawal subscale scores were low across time. The trained observer could not tell the difference between drug conditions (i.e., remained blinded) as demonstrated by the absence of differences in mean objective opioid adjective agonist subscale scores between conditions.

Plasma drug analyses

All available alfentanil plasma samples (N=214) were used. Mean peak plasma alfentanil concentration (combining all alfentanil sessions) was 18.9 ng/mL (+/− 12 ng/mL SD) and occurred on average at 34 minutes (median 15 minutes, range 15–90) post IM injection (analysis not shown). However, there was a large range in plasma alfentanil levels indicating that there was a difference in drug absorption between individuals (Table 2).

Physiological measures and side effects

There were differences between alfentanil and diphenhydramine on diastolic blood pressure (DBP), skin temperature, and respiratory rate (RR) measurements after drug exposure (Table, Supplemental Digital Content 1 which illustrates exploratory multivariable analyses); opioids are known to affect each of these measures. As expected, there was also a difference in pupil diameter for the alfentanil as compared to diphenhydramine group (Table 2), and there were condition-by- time effects for this outcome (Table, Supplemental Digital Content 1 which illustrates exploratory multivariable analyses). One participant had a RR of 6 breaths per minute after receiving alfentanil but did not have a drop in oxygen saturation and did not require medical intervention. No person dropped out of the study due to study medication side effects.

DISCUSSION

With the rise in opioid prescriptions for treatment of chronic pain, there has been increasing attention to the long-term physiological effects of opioid use. One area of particular interest has been opioid-induced hyperalgesia (OIH). Hyperalgesia has been suggested using standard experimental pain techniques in chronic pain patients and persons with opioid dependence in cross-sectional studies examining responses to experimental pain testing compared to matched healthy controls [9, 11, 43, 44]. However, these studies do not establish a causal relationship between chronic opioid use and hyperalgesia. Few prospective studies

have followed cohorts before and after opioid use to help establish causality. These types of studies are difficult to design and complete, especially in the recruitment of an adequate number of opioid naïve participants. A human model of OIH that closely mimics chronic opioid use without inducing opioid physical dependence would allow for (1) a better understanding of OIH, (2) a way to study treatment options for OIH, and (3) an estimate of the relative risk of OIH with various opioid analgesic agents.

The present experiment was designed to test the effects of repeated alfentanil IM injections on cold pressor and pressure pain sensitivity over 8 experimental sessions and determine if OIH could be demonstrated. This experimental design was unique in that it performed successive cold pressor and algometer pain testing repeatedly (total of 56 times) over 4–5 weeks on the same individual. Prior studies of single doses of parenteral remifentanil, fentanyl and morphine had demonstrated biphasic temporal responses to opioid exposures - showing first acute antinociceptive responses and then pronociceptive responses with a final resolution of each response at the end of session [7, 16, 17, 45, 46]. Analgesia, as evidenced by an increase in cold PTol and pressure PThr, was seen in the alfentanil group. There were mean decreases from baseline cold PTol seen in most sessions, usually at the 180 or 480 minute marks after alfentanil administration. This finding provides some evidence of OIH. However, hyperalgesia was not consistently seen across alfentanil sessions at these time points, and the magnitude of hyperalgesia was similar to diphenhydramine sessions.

There were several important findings as a result of this study. A finding relevant to future drug abuse and pain clinical trials was the lack of change in abuse liability measures across the 8 sessions in the alfentanil group. This population consisted of healthy males with no current DSM-IV TR [47] substance use disorder, although 5 males reported past experimentation with illicit drugs. There were differences between groups on drug LIKING, HIGH, and GOOD EFFECTS VASs, but scores did not increase over sessions. In the current experiment, participants were not given a range of alfentanil doses to assess a possible dose response curve with repeated exposures. However, other experimenters have shown healthy populations report significant VAS ratings for HIGH and LIKING when given full and partial mu opioid receptor agonists [48, 49] that do not consistently increase with higher doses.

Looking at baseline pain testing across sessions, this study demonstrates the stability of pain thresholds for both the cold pressor and algometer pressure pain models within the same participant over 4–5 weeks. There was a small increase in mean baseline cold pain tolerance in both conditions; this was not surprising, given past studies showing habituation to the cold pressor cardiovascular response in healthy volunteers [50, 51].

In this first step toward development of a human repeated opioid exposures model, this study was unable to demonstrate OIH. This may have been due to several limitations of the experimental design – single alfentanil injections given twice weekly during 480 minute sessions for 4 weeks. More frequent injections, higher alfentanil dosages, and prolonged monitoring (> 480 minutes) in a given session may have been needed. Animal studies, for example, have found daily heroin injections induce OIH [7]. However, higher doses and more frequent exposure to opioids enhance the risk of dependency. In this study, there was some evidence of analgesic tolerance by session 7, so participants may have been at higher risk for opioid physical dependence had the trial length or frequency of injections increased. In addition to potential ethical arguments against these models, there are several practical considerations. Six persons dropped out of this study due to scheduling conflicts; requiring a person to be in a laboratory for 480 minutes twice weekly for 4 straight weeks can be burdensome. Increasing such a time commitment could limit the potential study population and the generalizability of this OIH model. Finally, human studies of single opioid injections have only shown hyperalgesia during withdrawal [16, 17] and no evidence of withdrawal was

seen in this experiment. As alfentanil was still found in some plasma samples at 480 minutes, pain testing beyond this time point may have shown OIH.

Another issue might be related to the choice of diphenhydramine as an active placebo. Some evidence suggests that diphenhydramine may increase hyperalgesia, as was shown in an intradermal capsaicin pain model in humans [29]. The current results suggest that repetitive doses of diphenhydramine may be associated with hyperalgesia as measured by CPT. Future efforts should consider an inert placebo such as saline. Additionally, as opposite sex research assistants administered the pain testing, social desirability may have had a mediating effect on pain responses from the male participants [52]. Finally, a rigorous review found weak evidence in favor of OIH in humans [53]. Results in past studies showing abnormal pain sensitivity in chronic pain patients or opioid dependent patients as compared to healthy controls might not have been caused by chronic opioid exposure, but instead, could represent a risk factor for the development of these chronic conditions, or represent opioid tolerance. Only larger scale prospective cohort or clinical studies involving chronic pain patients treated with or without opioids can help to answer this question.

This study has several additional limitations to consider. First, the sample size was intentionally small as this was to be a preliminary proof-of-concept step in the development of a human OIH model. In addition to power issues, the small sample size increased threats to validity related to potential unbalanced groups. For example, we observed a difference in age between the two groups. Older age has been shown to decrease cold pain threshold and tolerance [54]. The two groups also had differences in racial self-identification. Racial differences in pain sensitivity have been well-described [40, 55]. Although we endeavored to statistically control for group differences on mean age, race and neuroticism (Table, Supplemental Digital Content 1 which illustrates exploratory multivariable analyses), the small sample size limits confidence in our ability to minimize confounds. Second, there was a variable rate of absorption between participants receiving IM alfentanil administration, a known property of this route of administration [25]. The total absorbed dose may not have been high enough to induce OIH, especially as no episodes of vomiting occurred amongst the alfentanil group, a common side effect at moderately high alfentanil doses [56].

In conclusion, this experiment demonstrated the relative safety of administering parenteral doses of opioids repetitively to healthy males. It also provided important evidence towards the stability of pain thresholds after a high number of cold and pressure pain tests over 4–5 weeks. Both of these findings can help researchers design future pain experiments after repeated opioid doses. However, studies of OIH in humans should consider designs that may maximize the demonstration of this phenomenon, if it does exist in humans. As the number of opioid prescriptions continue to increase, these experiments can better inform the long-term use of these medications in terms of both abuse potential and possible changes to pain sensitivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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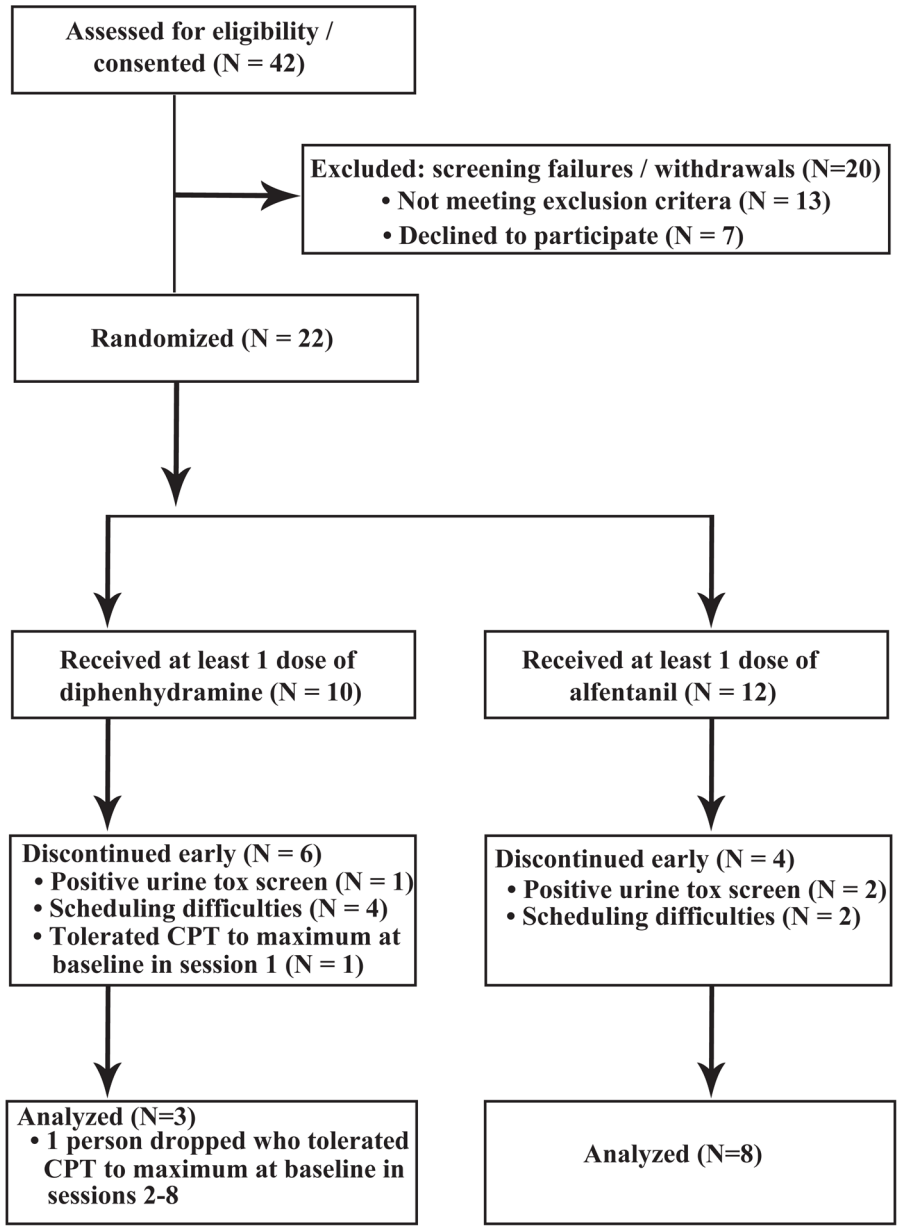

Figure 1.
CONSORT diagram of eligible participants. CPT=cold pressor test.

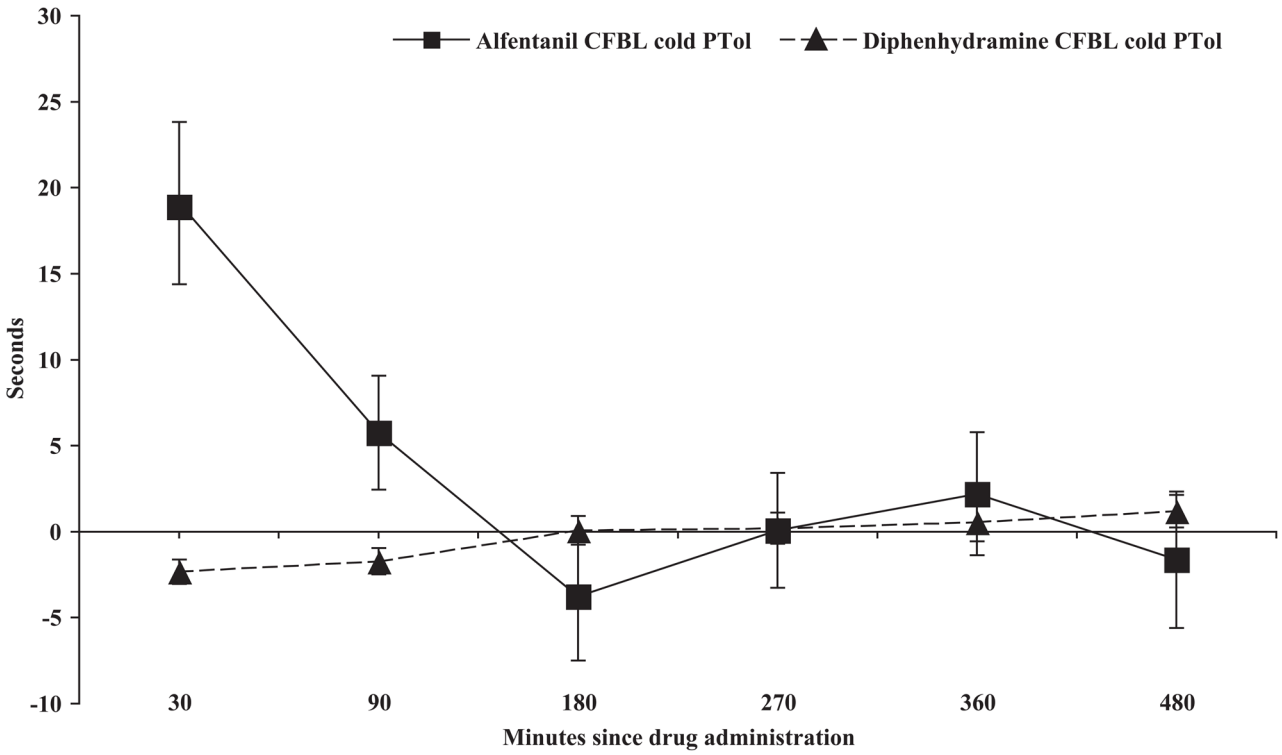

Figure 2.
Mean change from baseline cold pain tolerance (CFBL cold PTol) within session.

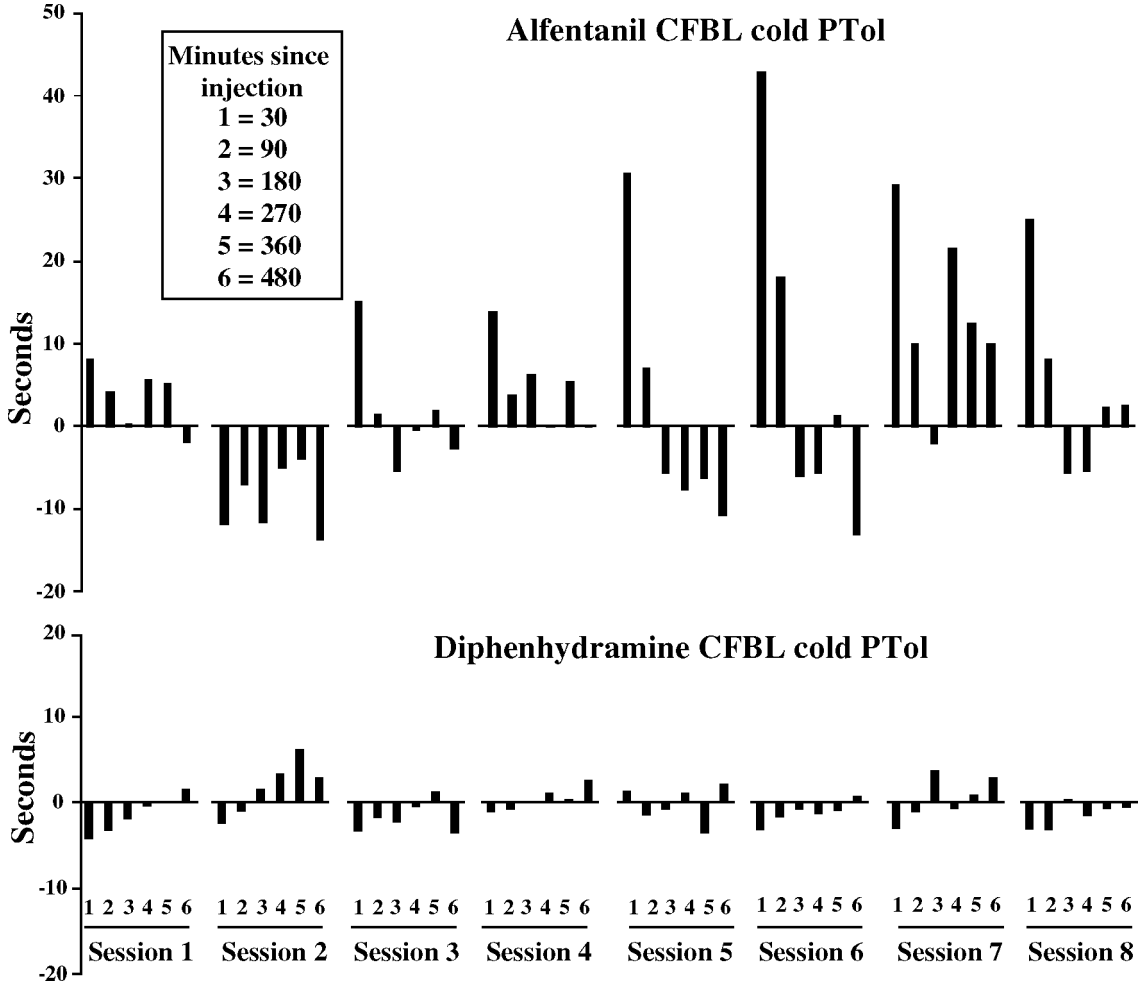

Figure 3.
Mean change from baseline cold pain tolerance (CFBL cold PTol) across sessions.

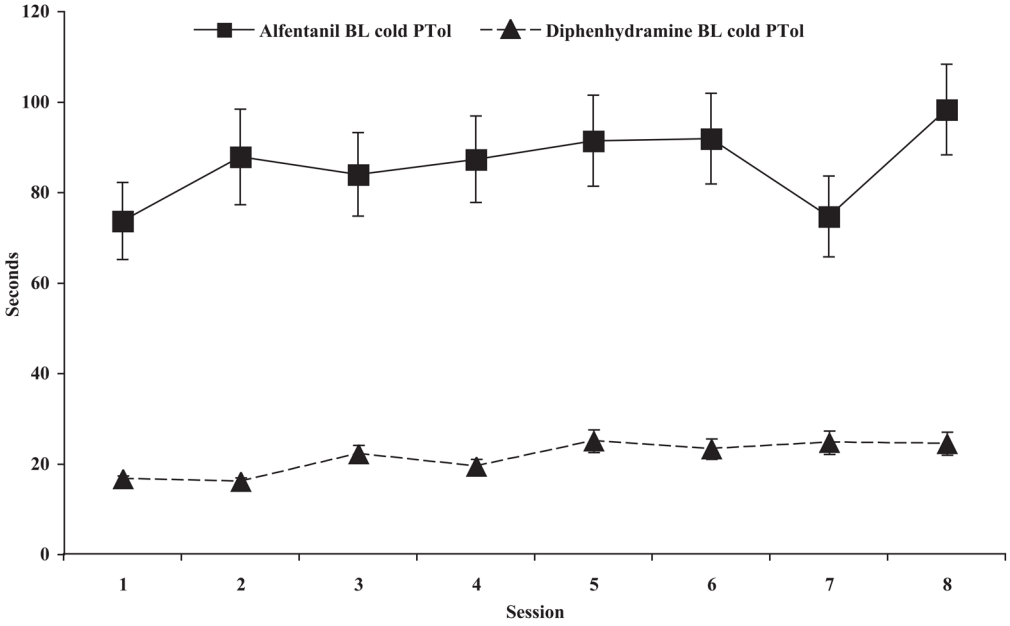

Figure 4.
Mean baseline (BL) measure of cold pain tolerance (cold PTol) across sessions.

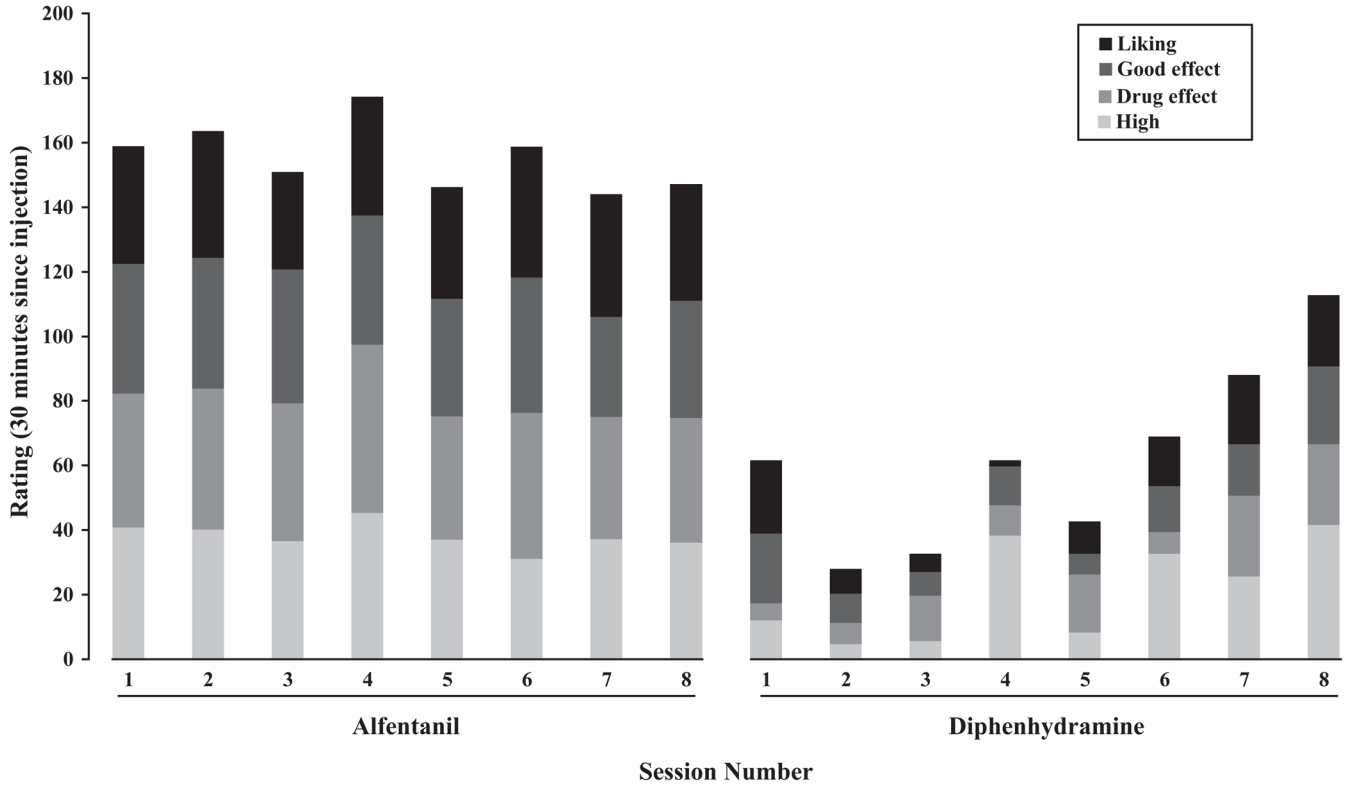

Figure 5.
Aggregate ratings of abuse liability measures at peak drug effects (30 minutes after injection).

Table 1

Description of Study Participants.

	Alfentanil (N=8)	Diphenhydramine (N=3)	Analyzed (N=11)	Non-analyzed (N=11)
Race				
Caucasian (%)	75	0	55	46
African American (%)	12.5	100	36	36
Other/Unknown (%)	12.5	0	9	18
Age (years +/−SD)	35 (14)	46 (2.6)	38 (13)	35 (10)
BMI (+/−SD)	26 (2.8)	30 (0.2)	27 (2.7)	25 (3.3)
Alcohol Beverages per Week (+/−SD)	5.1 (4.3)	1.3 (2.3)	4.1 (4.1)	1.7 (3.8)
Past Illicit Substance Use (%)	63	67	64	18
T-scores of NEO-PI (+/−SD)				
Neuroticism	53 (13)	41 (12)	49 (13)	37 (9.2)
Extroversion	49 (8.2)	51 (10)	49 (8.3)	57 (9.5)
Openness	55 (7.1)	48 (6.6)	53 (7.4)	53 (13)
Agreeableness	47 (11)	57 (16)	49 (12)	53 (12)
Conscientiousness	46 (8.5)	58 (13)	50 (11)	60 (9.8)
BL Vitals				
SBP – mmHg (+/−SD)	117 (21)	122 (10)	118 (18)	120 (13)
DBP – mmHg (+/−SD)	65 (6.8)	69 (5.3)	66 (6.5)	66 (8.5)
HR – beats/min. (+/−SD)	65 (8.4)	70 (9.6)	67 (8.4)	71 (9.6)
BL Pupil Diameter – mm (+/−SD)	4.6 (0.9)	3.6 (0.4)	4.3 (0.9)	4.4 (0.8)
BL Pain Testing				
Pressure PThr – kPa (+/−SD)	295 (76)	339 (207)	307 (114)	428 (244)
Cold PThr – sec. (+/−SD)	13 (5.6)	10 (3.4)	12 (5.1)	62 (145)
Cold PTol – sec. (+/−SD)	74 (68)	17 (3.5)	58 (62)	98 (143)

BMI=Body Mass Index. SD = standard deviation. NEO-PI = NEO Personality Inventory. BL = baseline. SBP = systolic blood pressure. DBP = diastolic blood pressure. HR = heart rate. PThr = pain threshold. PTol = pain tolerance.

Table 2

Mean Values and Ranges of Pain and Abuse Liability Outcomes Collapsed Across Sessions.

	Alfentanil													
	Baseline		30		90		180		270		360		480	
	M	R	M	R	M	R	M	R	M	R	M	R	M	R
Pressure PThr	308	119–1110	314	134–1090	295	130–1090	292	125–1045	293	121–1090	295	117–1090	295	110–1090
Cold PThr	16.1	4.9–65.1	20.7	4.6–73.6	18	2.9–67.1	15.5	3.6–73	17.6	3.1–67.9	18.4	4–65.9	18	3–98
Cold PTol	86.2	9.9–232	105.3	10.5–300	92	9.9–247	82.5	9.4–195	86.3	9.2–219	88.4	8.4–216	84.1	9.3–300
Pupil	4.8	2.8–7.9	3.7	2.3–6.7	3.9	2.3–7	4.3	2.6–7.3	4.6	2.7–7.8	4.7	2.7–7.7	4.9	2.9–7.2
High	--	--	38.1	0–85	22.9	0–82	11.8	0–54	7.4	0–54	3.9	0–45	2.1	0–19
Drug Effect	--	--	42.5	3–89	27.9	0–86	17.1	0–82	7.8	0–52	4.8	0–39	2.6	0–21
Good Effect	--	--	38.6	0–84	22.6	0–65	12.5	0–53	7.8	0–48	7.6	0–50	3.5	0–47
Bad Effect	--	--	13	0–83	15.2	0–89	13.2	0–66	7.7	0–52	7.5	0–50	4	0–49
Liking	--	--	36.4	0–71	24.8	0–54	17.5	0–53	13.1	0–50	14.3	0–50	12.1	0–49
Sick	--	--	5.2	0–73	4.6	0–51	2.8	0–22	1.8	0–21	2.8	0–43	1.8	0–14
Subj. Ag.	--	--	13.2	0–27	11.7	2–23	9.8	2–19	8.7	0–19	8.7	1–21	9	1–18
Subj. Withd.	--	--	3.8	0–13	3.4	0–26	3.1	0–9	2.6	0–9	2.8	0–10	2.3	0–12
Obj. Ag.	--	--	9.1	2–21	8.2	3–13	8	3–14	7.7	3–13	7.5	3–13	7	1–12
Obj. Withd.	--	--	3.3	0–9	3.3	0–9	3.1	0–10	3.3	0–8	2.9	0–6	2.9	0–9
Alf. Conc.	--	--	14.3	1.3–38	9.1	0.5–19.2	5.6	0.3–17	3.3	0.2–6.7	2.5	0.1–5.3	1.4	0–4.1
	Diphenhydramine													
Pressure PThr	320	174–578	291	158–559	297	156–551	285	147–512	276	136–488	303	135–603	282	163–594
Cold PThr	11.5	5.9–22.2	8.6	4.4–22.5	8.9	4.4–20.7	9.5	3.3–21.6	9.7	4.2–25.8	9.5	4.2–18.6	9.9	2.4–21.6
Cold PTol	21.5	9.1–38	19.2	7.1–38.7	19.8	7.8–39.7	21.6	8.3–47.5	21.7	8.6–41	22	8.5–41.8	22.7	8.4–48.2
Pupil	3.5	3–4	3.2	2.4–3.9	3.4	2.5–4	3.4	2.8–3.9	3.3	2.6–3.9	3.4	2.7–3.8	3.6	3.1–4.2
High	--	--	21.1	0–99	16.5	0–64	14.4	0–81	12	0–79	5.6	0–33	3.1	0–15
Drug Effect	--	--	13.8	0–68	14.3	0–74	9.8	0–45	7.8	0–44	6.2	0–39	2.5	0–16
Good Effect	--	--	13.8	0–63	11.7	0–62	8.9	0–47	7.7	0–39	7.1	0–44	3.2	0–16
Bad Effect	--	--	2.4	0–19	1.5	0–9	1.5	0–8	2.3	0–12	1.9	0–22	1.1	0–6
Liking	--	--	13.3	0–61	11.1	0–42	13.6	0–80	7.7	0–38	6.2	0–56	5	0–41
Sick	--	--	2.7	0–13	2.8	0–27	2.1	0–19	4.9	0–70	1.6	0–11	1.3	0–6

	Alfentanil													
	Baseline		30		90		180		270		360		480	
	M	R	M	R	M	R	M	R	M	R	M	R	M	R
Subj. Ag.	--	--	5.7	0–12	6.1	0–26	4.8	0–17	4.5	0–7	3.9	0–7	3.2	0–6
Subj. Withd.	--	--	2.5	0–13	3.1	0–24	2.3	0–20	1.5	0–4	0.8	0–3	0.4	0–4
Obj. Ag.	--	--	9.3	3–17	8.3	0–14	7.5	0–12	7.1	0–12	7	0–12	5.7	0–10
Obj. Withd.	--	--	3.7	0–10	3.6	0–9	3	0–8	2.4	0–8	1.9	0–6	1.3	0–4

Column headers are minutes since IM injection of study medication. M=mean value of outcome at each time point; R=range (minimum to maximum); Pressure PThr=pain threshold (kPa); Cold PThr = pain threshold (seconds); Cold PTol= pain tolerance (seconds); Pupil=pupil diameter (mm); High, Drug Effect, Good Effect, Bad Effect, Liking, Sick were visual analog scales (0–100); Subj./Obj. Ag.= subjective/objective opioid agonist adjective subscale scores; Subj./Obj. Withd.= subjective/objective opioid withdrawal adjective subscale scores; Alf. Conc.=alfentanil plasma concentration (ng/ml).