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Effect of Intravenous Alfentanil on Nonpainful Thermally Induced Hyperalgesia in Healthy Volunteers

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Abstract

Experimental interventions that activate specific components of clinical pain are necessary for characterization of underlying mechanisms and pharmacology. Cutaneous hyperalgesia has been described that uses nonpainful heat to induce secondary hyperalgesia. This study evaluated the effect of intravenous alfentanil on experimental cutaneous hyperalgesia created using this method. Eighteen subjects participated in a randomized, double-blinded, placebo-controlled crossover study consisting of 2 sessions, 1 with alfentanil and 1 with placebo. Using a computer-controlled infusion pump, alfentanil or matching placebo was maintained at a constant plasma level of 75 ng/mL for 1 hour followed by the application of a 40°C heat stimulus to the right thenar eminence for 15 minutes. The temperature was raised by 1°C every 15 minutes until the subject reported pain or 45°C was reached. After the end point was reached, the temperature was maintained, and repeat testing was performed. The nonpainful heat created an area of secondary cutaneous hyperalgesia and significant decrease in mechanical pain threshold on heat-treated right vs untreated left during placebo administration. Alfentanil prevented the hypersensitivity when compared to placebo ($P < .05$) but failed to reduce the area of secondary hyperalgesia created by nonpainful heat when compared to placebo ($P = .06$). Neither alfentanil nor the heat lamp treatment showed any significant effect on other neurosensory measures. This study demonstrated a reliable production of cutaneous hyperalgesia using a nonpainful stimulus that is affected by the systemic delivery of alfentanil. This model for human cutaneous experimental pain may be a useful method for scientific characterization of analgesics.

Keywords

opioid, experimental, heat, pain, research

The manifestation of clinical pain involves numerous complex mechanisms that are difficult to isolate in the clinical setting (eg, tissue and nerve injury accompanied by inflammation).[1] Furthermore, patients treated for pain often receive multidrug therapies, and it is difficult if not impossible to organize controlled crossover designs with the same clinical subject.[2,3] Due to the complex mechanisms for pain, experimental interventions that target specific components of the process allow researchers to better characterize the etiological components of pain.[4] Human experimental pain models that allow the testing of analgesic drugs in healthy volunteers serve to allow stimulation of specific aspects of the pain pathway so that they may be studied independently. Additionally, crossover designs can be easily conducted, and comparisons can be drawn between human and animal models, to define in parallel the pharmacology and physiology of the pain state. The ideal experimental pain model allows the researcher to obtain proof of drug efficacy prior to costly clinical trials in pain patients and would be reliable, noninvasive, and minimally painful in nature. Such a model could successfully bridge the gap between experimental pain in animals and clinical pain in humans.[5]

Human cutaneous experimental pain models using intradermal capsaicin have been extensively conducted in humans, and the pharmacology of this experimental pain model has been investigated with various classes of interventions including opioids, NMDA antagonists, sodium channel antagonists, tricyclic antidepressants, nonsteroidal anti-inflammatory agents, and α_2 agonists. However, numerous studies show that this model of experimental pain is significantly resistant to drug interventions and may underestimate the efficacy of drugs in clinical pain states.[6–8] One of the criticisms of these studies is that the painful stimulus that results from the intradermal capsaicin is too intense and does not mimic the pain of chronic pain states. Other models have been investigated in an attempt to obtain an experimental method that will accurately quantify the analgesic effects of opioids and other drug interventions. A model

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using topical capsaicin and heat sensitization, followed by rekindling with a nonpainful heat stimulus, has been used; however, the pharmacology of this model is very similar to that of the intradermal capsaicin model.[10–12]

A model of cutaneous hyperalgesia has been described that uses nonpainful heat alone to induce secondary hyperalgesia in humans.[13] There is a need to evaluate this new model to determine if it mimics chronic pain states. As opioids have been shown to significantly affect the pain and hyperalgesia of intradermal capsaicin,[7,8] it follows that an opioid would be a reasonable drug to start with to investigate this new model. We hypothesized that intravenous alfentanil would decrease the area of hyperalgesia induced by nonpainful heat.

Methods

After giving informed written consent, 18 healthy volunteers (13 male and 5 female, ages 23 to 57) participated in a 2-session protocol conducted in accordance with the Helsinki Declaration and approved by the Institutional Review Board at the University of California, San Diego. Inclusion criteria were age 18 and above. Exclusion criteria were (1) pregnancy, (2) allergy to alfentanil, (3) history of drug abuse, (4) current painful condition, (5) current use of analgesics for treatment of pain, and (6) lack of ability to understand the experimental protocol or to adequately communicate in English. Nineteen subjects were evaluated for the study, with 1 subject excluded for bradycardia and heart murmur during the screening physical exam. The volunteers were healthy, ages 18 to 65, had no history of drug abuse, allergy to alfentanil, or current painful condition. Each subject underwent 2 sessions, which were randomized based on a computer-generated randomization schedule, blinded to both the patient and experimenter, and separated by 1 month.

An experimental protocol for each subject was as follows. On day 1, the subject received a brief explanation of the study, gave informed consent, and underwent screening and physical examination including assessment of vital signs to determine eligibility to participate in the study. Women were given urine pregnancy tests to confirm lack of pregnancy. After clearing all screening questionnaires, the patients were familiarized with the instruments to be used: von Frey hairs, foam brush, thermal sensory analyzer, and heat lamp. They were familiarized with the sensations of von Frey and foam brush stroking and were also instructed on how to use the visual analog sliding scale to measure their pain, with 1 side of the 10-cm scale labeled "no pain" and the opposite labeled "worst imaginable pain."

Subjects then underwent baseline neurosensory testing as described below, and subsequently, a 20-gauge venous cannula was inserted into a convenient left arm vein and connected to a computer-controlled infusion pump, and an intravenous infusion of lactated Ringer's solution at a rate of 50 mL/h was maintained while a plasma concentration of 75 ng/mL of alfentanil was reached and maintained by the computer-controlled infusion pump as calculated by age, weight, and rate of alfentanil metabolism. One hour after the beginning of the infusion, a plasma sample was drawn from the right arm for measurement of plasma drug concentration, and vital signs were recorded. Subjects were asked if they were experiencing any of the following side effects: (1) nausea, (2) sedation, (3) light-headedness, (4) other. Any side effects reported were rated on a scale of 0 to 10 with 0 being no side effect and 10 being the worst side effect imaginable. Drug administration then continued for the duration of the experiment.

The patient's right arm was positioned comfortably on a foam pillow, and a nonpainful heat stimulus was applied to the dorsal aspect of the right thenar eminence using a focused heat lamp with a lit area approximately 1 cm in diameter. Skin temperature was measured using a calibrated cutaneous temperature probe. Initially, the temperature was set to 30°C, and then raised to 40°C, where it remained for 15 minutes. At the end of this period the skin temperature was raised by 1°C and maintained for an additional 15 minutes. This pattern of stimulation continued until the subject first registered a pain sensation, or a temperature of 45°C was reached, at which time the temperature was maintained while testing was conducted around and within the area of stimulation.

Sensory tests were then repeated as described below. On completion of the final sensory tests, the infusion was stopped, and the patient was monitored for 1 to 2 hours before being released. The second visit repeated all of the above-described methods and occurred at least 1 month later.

Neurosensory testing was performed (1) prior to infusion on dorsal aspects of right and left thenar eminences, (2) following both infusion and heat stimulation of the dorsal aspect of the right thenar eminence in the area of direct heat stimulation, and (3) following infusion in the comparable area of the dorsal aspect of the left thenar eminence, which did not receive a heat stimulus. Neurosensory testing consisted of 4 measurements as described below: (1) warm and cold sensation, (2) warm and cold pain, (3) touch, (4) mechanical pain. Throughout the experiment, whenever the patient reached a pain threshold, he/she was asked to rate the pain using the sliding visual analog pain scale. All neurosensory testing was conducted within the

heat-treated area when applicable or on the comparable location for control measurements.

Warm and cold sensations were measured using a Thermal Sensory Analyzer (Medoc Advanced Medical Systems, Minneapolis, Minnesota) with a thermode applied to the dorsal aspect of the hand. The probe was 2 cm × 2 cm and had a 1°C/s rate of change for warm and cool sensation and 1.5°C/s rate of change for the heat and cold pain. The patient held a button with the opposite hand and was instructed to depress it at the first sensation of warmth or cold; this subsequently reversed the temperature change, returning to a neutral temperature of 32°C. Warm and cold pain thresholds were determined in a similar manner, with the end point instead being pain, and the subject also registering a pain score by visual analog scale. Hot and cold sensation was measured 4 times, with the average being recorded, and hot and cold pain threshold was measured 3 times, with the average also being recorded.[14]

Touch was measured using von Frey hairs. Calibrated von Frey hairs are filaments of varying size that deliver a precise force (in mN) when pressed onto the subject's skin. Filaments in increasing and decreasing size were pressed onto the dorsal aspects of the thenar eminences, and the subject was instructed to report if the stimulus was felt. Thresholds were measured as the middle between the strongest stimulus not felt in 3 trials and the weakest stimulus felt. Mechanical pain was also measured using von Frey hairs. The same method as described for touch was used except the end point was pain, and a visual analog scale was reported. Temporal summation pain using a 5.12 von Frey was then tested by touching the same spot on the back of the hand 5 times, at a rate of 1/s, with a VAS recorded. Pain elicited by foam brush stroking was also measured at baseline.[15]

Immediately on completion of heat lamp stimulation (ie, registration of heat pain or maximum temperature stimulation), areas of cutaneous allodynia and hyperalgesia were mapped. The region of hyperalgesia was established with a 5.18-mN von Frey hair, and the area of allodynia with a foam brush gently stroked on the skin. These stimuli began in an area of skin that did not produce pain, away from the center of heat stimulation, and were then repeated tangentially toward the center of the painful area until the subject reported pain or tenderness. That site was marked on the skin, and a new series was started from the periphery at a different angle until 4 determinations of the borders of allodynia and hyperalgesia were outlined on the skin. These borders as well as the flare response were then traced onto a transparency for area determination. The neurosensory thresholds were then established at the center of the site of heat simulation for determination of primary hyperalgesia.

JMP Pro software (SAS Institute, Cary, North Carolina) was used for statistical analysis. Sample size determinations for type I error rate = 0.05 and type II error rate of 0.20 (power = 0.80) were determined, with a sample size of 18 determined to be adequate. Data collected from the 18 subjects were initially analyzed as a group, using simple comparison of means for continuous variables such as temperature and areas and means for noncontinuous variables such as von Frey thresholds and time of heat lamp exposure. Several measures were identified as possible indicators of the ability of the heat lamp to induce hyperalgesia by comparing heat lamp–treated right to untreated left. Possible drug effects were identified by comparing placebo to alfentanil pre– and post–heat treatment on the right. Mechanical sensory stimulation by von Frey filament, mechanical pain sensation by von Frey filament, von Frey mapping area, and time registration of a painful sensation with the use of the heat lamp were all further investigated for significance due to promising trends in mean values. Temperature sensitivity and pain thresholds did not appear to be significantly affected by drug administration or heat lamp stimulation. Significance was then established using paired ranking statistics and a P-value $< .05$ for all noncontinuous variables (all except mapped areas). For continuous variables (mapped areas) analysis of variance and t-test were used to determine significance.

Results

Heat lamp treatment of the dorsal aspect of the right thenar eminence resulted in a significant area of secondary hyperalgesia as demonstrated by von Frey mapping, as well as primary hyperalgesia as demonstrated by a significant increase in mechanical sensory threshold and a significant decrease in mechanical pain threshold relative to the untreated left (Figures 1 and 2). There was no significant change in temperature sensation or temperature pain thresholds comparing the heat-treated right to the untreated left (Table 1). Pain scores for all measures, recorded using a 10-cm visual analog scale, were unable to detect any significant change in quantity of pain associated with the area of hypersensitivity created by the heat lamp.

Mechanical sensation elicited on the heat-treated right thenar eminence using von Frey filaments showed a significant increase ($P < .05$) in threshold when compared to the untreated left in the placebo group. There was no effect of alfentanil on the increased mechanical threshold (Figure 1). Mechanical pain threshold elicited by von Frey on the heat-treated right thenar eminence showed a decrease ($P < 0.05$) in threshold when compared to the untreated left. This effect was reversed by administration of alfentanil (Figure 2).

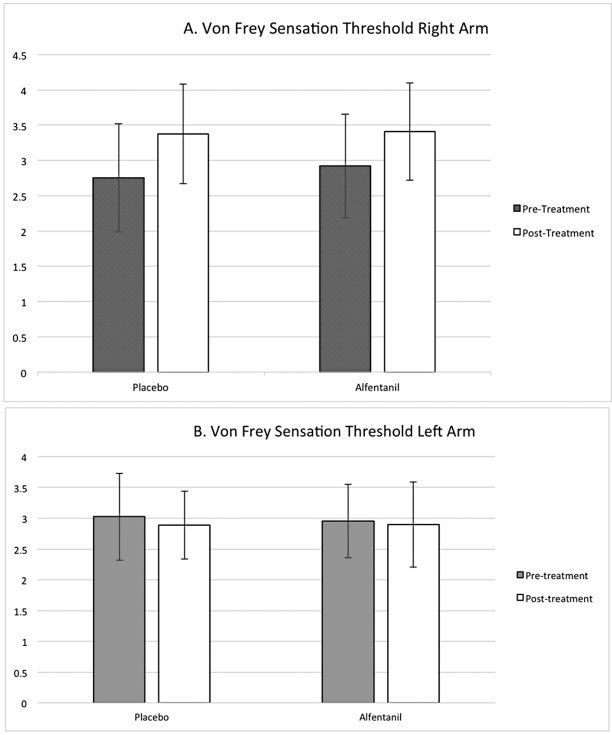

Figure 1. The effect of a nonpainful heat stimulus on mechanical sensation. The application of a nonpainful heat stimulus resulted in a significant increase in strength of von Frey stimulus needed to register sensation in the heat-treated right thenar eminence (A) vs the nontreated left (B) during placebo administration. These heat lamp effects were not abolished by the administration of alfentanil. N = 18 in each group.

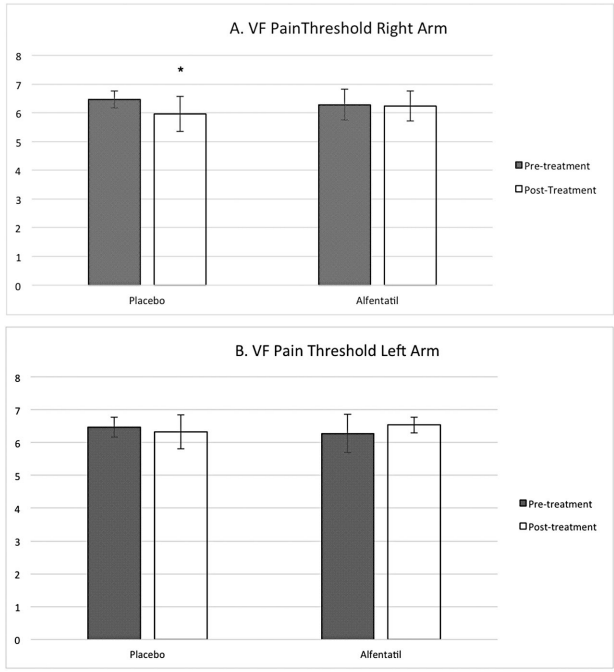

Figure 2. The effect of a nonpainful heat stimulus on mechanical pain. The application of a nonpainful heat stimulus resulted in a significant decrease in the strength of von Frey stimulus needed to register pain in the heat-treated right thenar eminence (A) vs the nontreated left (B) during placebo administration. These heat lamp effects were abolished by the administration of alfentanil. N = 18 in each group. VF indicates von Frey.

Alfentanil significantly increased the time to registration of a painful sensation from heat lamp stimulation. Eleven of 18 patients had an increase in lamp pain time with alfentanil vs placebo, a significant finding ($P < .05$). Mean time to lamp pain for placebo was 48 ± 32 minutes (median with interquartile range was 39 [21–86]), and for alfentanil it was 67 ± 30 (median with interquartile range was 90 [44–90]). The area of secondary hyperalgesia was mapped using a 5.18-mN von Frey filament and was detectible in heat lamp–treated right vs untreated left, indicating the ability of the heat lamp to create an area of secondary hyperalgesia. This area of hyperalgesia was not significantly reduced in alfentanil vs placebo, but this statistic did approach significance ($P = .06$ by paired t-test). Other mapped areas, allodynia by foam brush and flare by visualization, showed no significant difference in placebo vs alfentanil groups (Figure 3). When the area of secondary hyperalgesia was compared to heat lamp time, there was no significant correlation in the placebo (r = –0.23), alfentanil (r = –0.15), or pooled data (r = –0.25).

Side effects of heat-lamp treatment included reports of redness and mild tenderness of the heat lamp site in most cases similar to that of a mild sunburn, and 1 report of blister formation at the stimulation site. Side effects of intravenous alfentanil included sedation, light-headedness, and nausea (Figure 4). Two patients received antiemetic medication for nausea during 1 of

Table 1. Summary of Sensory Thresholds

	Cool Sensation °C		Warm Sensation °C		Cool Pain °C		Warm Pain °C	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Placebo-left/control	30.2 (1.7)	28.0 (3.0)	35.0 (1.6)	35.7 (2.5)	14.9 (11.8)	14.0 (10.0)	44.5 (4.3)	44.7 (4.4)
Placebo-right/heat	30.3 (1.4)	29.0 (2.1)	34.5 (1.7)	36.3 (2.8)	12.5 (11.2)	13.3 (11.0)	44.6 (3.9)	45.3 (3.2)
Alfentanil-left/control	29.2 (2.0)	27.2 (2.8)	35.7 (2.8)	35.8 (2.2)	13.9 (11.7)	12.3 (11.0)	45.3 (3.9)	45.5 (4.1)
Alfentanil-right/heat	29.5 (2.3)	28.7 (1.9)	35.1 (1.8)	36.5 (1.9)	11.9 (11.4)	11.4 (11.3)	45.3 (4.0)	46.1 (3.9)

Values are means (standard deviations).

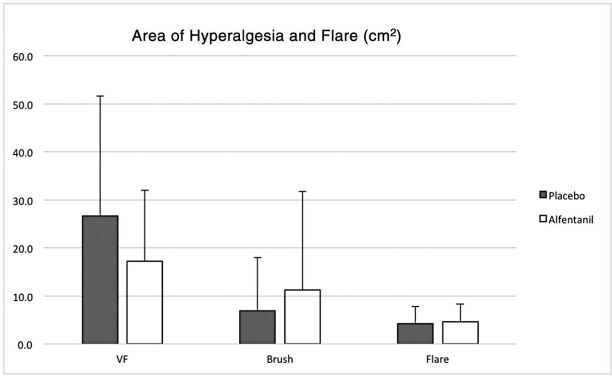

Figure 3. The effect of alfentanil on nonpainful heat-induced secondary hyperalgesia. The area of cutaneous secondary hyperalgesia measured by von Frey stimulation and foam brush as well as the flare response was not significantly reduced in the alfentanil group when compared to placebo ($P = .06$). N = 18 in each group.

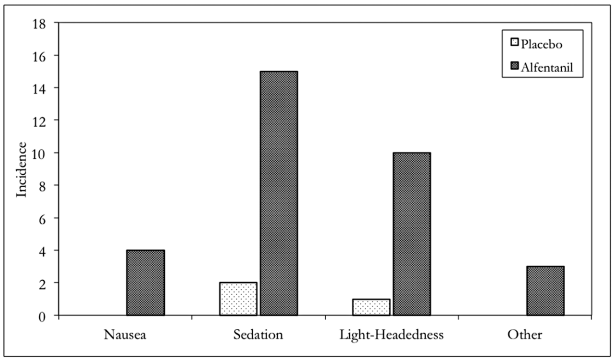

Figure 4. Side effects of alfentanil. Number of subjects experiencing side effects after intravenous alfentanil as compared to placebo. N = 18 in each group.

their treatments, and 2 patients experienced episodes of emesis secondary to nausea. All patients were followed up 2 days posttreatment, with no patients reporting any significant discomfort at the stimulation site or any residual nausea, vomiting, or other problems posttreatment.

Discussion

The induction of an area of secondary hyperalgesia with nonpainful heat constitutes a safe and reliable method of inducing cutaneous experimental hypersensitivity and pain in healthy volunteers. In a previous study the ability of nonpainful heat to induce an area of hyperalgesia was demonstrated,[13] but the ability of an opiate to alter this area had not previously been studied. The purpose of this study was 2-fold: (1) to induce an area of hyperalgesia using nonpainful heat and (2) to detect differences in the character of the facilitated pain caused by the infusion of an opioid known to have clinical efficacy.

Most thermal models of human experimental pain use a controlled heat injury. The burn model involves the exposure of skin to a 47°C thermode for 7 minutes, which results in the report of pain, primary hyperalgesia, and secondary hyperalgesia.[16,17] In hairy skin it is thought that the heat used to induce the pain only activates C-mechano-heat nociceptors because A-mechano-heat nociceptors (AMH) are activated only by heat stimuli above 51°C.[16,18] The burn injury results in pain, primary hyperalgesia to mechanical and thermal stimuli at the site of injury, and secondary hyperalgesia to mechanical stimuli only in surrounding tissues. In the area of primary hyperalgesia, nonnoxious heat results in pain (heat hyperalgesia mediated by C-mechano-heat nociceptors) and painful heat results in exaggerated reports of pain (heat hyperalgesia mediated by both C-mechano-heat nociceptors and AMH).[16,19,20] In contrast, after thermal injury to glaborous skin, hyperalgesia is thought to be due to sensitization primarily in AMHs.[21] The pharmacology of this model has been extensively studied. Intravenous ketamine has been shown to affect most of the components of this pain model,[22] whereas oral ibuprofen, oral gabapentin, and intravenous adenosine affected a single component of the model,[23–25] and intravenous morphine had no effect.[26] Alfentanil increased pain thresholds and decreased the area of secondary hyperalgesia.[27]

Another less-well-defined thermal model of human experimental pain uses ultraviolet-B radiation applied without physical contact to the subject's skin. This application results in an area of erythema with decreased mechanical and thermal pain thresholds. Unlike the burn injury model, there is minimal pain during the application of the ultraviolet-B and no ongoing spontaneous pain. The stimulus results in primary hyperalgesia only, although some have reported short-lasting secondary hyperalgesia.[28] This model is sensitive to the effect of the opioids,[29,30] nonsteroidal anti-inflammator drugs,[31] and COX-2 inhibitors,[32] but gabapentin showed no effect.[30]

The model used in this study produced a heat-treated change in mechanical thresholds that was reversed by alfentanil and a secondary hyperalgesia that was not affected by alfentanil. There was no effect of heat treatment on thermal thresholds. Therefore, unlike the burn model and ultraviolet-B model, which produce both mechanical and thermal hyperalgesia, our current model only produces mechanical hyperalgesia. This suggests that in order to produce thermal hyperalgesia, AMH receptors have to be activated because we used temperatures that were not high enough to activate these fibers.

As expected, this model of nonpainful heat–induced hyperalgesia did not produce the robust pain, hyperalgesia, and flare induced by capsaicin models of experimental pain. Both intradermal and topical capsaicin

experimental models produce pain, secondary hyperalgesia, and a flare response.[33,34] The model used in this study produced a consistent secondary hyperalgesia and flare response, although the area of hyperalgesia and flare were much smaller than those produced by intradermal capsaicin. It is difficult to make comparisons on the area of hyperalgesia of the nonpainful heat model with the topical capsaicin models because the area of capsaicin applied to the skin is much larger than the area stimulated by the heat used in this model. The smaller areas of secondary hyperalgesia and allodynia seen in this study are likely explained by the much smaller C-fiber input into the central nervous system and lack of activation of AMH fibers as compared to capsaicin models. There are age-related differences in C- and A-fiber density, which could be a confounding factor. However, we did not see age-related differences in our study, which is probably due to the young mean age (32) and narrow range (23–57).[35] In addition, there is emerging evidence that differences in genetic expression in diseased skin and white blood cells as well as pharmacogenomic differences may account for differences in pain sensitivity. As genetic study methods evolve, it will be important to apply them to experimental pain models to explain interindividual differences.[36] We did not determine if the nonpainful heat stimulus would have resulted in secondary hyperalgesia and allodynia because we measured this only after the subjects' first report of pain. However, this report of pain was much lower than what is observed with capsaicin models.

Intradermal capsaicin results in a zone of primary hyperalagesia with lowered thresholds to both heat and mechanical stimuli and a zone of secondary hyperalgesia with lowered thresholds to mechanical stimuli only.[37–40] The nonpainful heat model used in this study resulted in a decrease in mechanical pain but not thermal pain thresholds, which suggests that the nonpainful heat model results in a secondary hyperalgesia and not a primary hyperalgesia. Primary hyperalgesia to heat stimuli develops at sites of injury and is mediated by sensitization of nociceptors.[16,41] There is no tissue injury in the zone of primary hyperalgesia after intradermal capsaicin, which suggests that the flare response is responsible for nociceptor sensitization. Although the nonpainful heat model results in a flare response, the absence of heat hyperalgesia suggests that it is not intense enough to induce nociceptor sensitization.

Previous studies have demonstrated a robust effect of opioids on the pain and hyperalgesia of intradermal and topical capsaicin models.[7,11,12] Studies have also demonstrated a dose-dependent effect of alfentanil on capsaicin-induced pain and hyperalgesia as well as differential effects on Aδ- and C-fibers.[9,42] We did not evaluate dose dependency in our study and chose to target 75 ng/mL plasma concentration of alfentanil based on our previous studies evaluating the effect of alfentanil on capsaicin-induced pain. These studies showed that 75 ng/mL reduced the pain and hyperalgesia induced by intradermal capsaicin.[6] In this study we only saw an effect of alfentanil on the mechanical pain induced by the heat stimulus but no effect on the secondary hyperalgesia. Although the heat stimulus increased mechanical (nonpainful) thresholds, this was not reversed by alfentanil. This is consistent with the specific effects of an opioid on C-fiber activity. Mechanical nonpainful stimuli are medicated by Aβ-fibers, which would not be affected by an opioid.[43] It should be noted that the fact that subjects spent a significantly longer time under heat lamp stimulation prior to registration of pain is a possible confounding variable. However, when the area of secondary hyperalgesia is correlated with heat lamp time, there is no significant correlation in the placebo ($r = -0.23$), alfentanil ($r = -0.15$), or pooled data ($r = -0.25$). Subjects spent a significantly greater time under the heat lamp during alfentanil treatment, likely due to its analgesic effect, and therefore had a longer period of stimulation when compared to placebo, which may contribute to the fact that reduction in area of secondary hyperalgesia approached but did not reach significance. Consistent with previous studies using intradermal capsaicin, alfentanil did not have an effect on the flare response.[7] This is to be expected because the site of action of alfentanil is central rather than peripheral.

There is evidence of sex differences in pain sensitivity as well as drug sensitivity.[44] We have shown sex difference using the sequential up-down method to evaluate the ED-50 of intravenous alfentanil on intradermal capsaicin pain. Females reported higher pain levels with capsaicin and required more alfentanil (M.S. Wallace et al, unpublished observations). We used both males and females in our study, which could confound the results given these differences and is a limitation of the study. However, the numbers were too small to detect any differences.

Experimental pain models used to demonstrate efficacy of analgesics such as capsaicin can cause significant discomfort to the subject and may be refractory to analgesic effect. Intraneural recordings have shown that both noxious heat and capsaicin activate C-fiber nocioceptors and result in the generation of areas of primary and secondary hyperalgesia. Duration of these areas has been shown to be dependent on the initial injury as well as ongoing nocioceptor input. Due to the similarities in mechanism of burn injury and capsaicin injection, it follows that drug responsivity should follow similar patterns.

Conclusion

In conclusion, we were able to create an area of hypersensitivity with nonpainful heat that can be mapped and quantified using von Frey stimulation. We were also able to show a significant reduction in this area with the administration of intravenous alfentanil. Comparing and contrasting this model with other well-described models of cutaneous hyperalgesia suggest that the different models are capable of activating varying groups of nerve fibers leading to different phenotypes. This may be important in future translational medicine studies on analgesic drugs.

Contributions

C.S. contributed to the conduct of the study, data collection, data analysis, and manuscript preparation. G.S. contributed to the study design, data analysis, and manuscript preparation. M.S.W. contributed to the study design, conduct of the study, data collection, data analysis, and manuscript preparation. All authors approved the final manuscript and reviewed the original study data and data analysis. Mark S. Wallace, MD, is the archival author.

Conflicts of Interest

None.

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