Published in final edited form as:

J Clin Pharmacol. 2017 September ; 57(9): 1207–1214. doi:10.1002/jcph.911.

EFFECT OF INTRAVENOUS ALFENTANIL ON NON-PAINFUL 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 non-painful heat to induce secondary hyperalgesia. This study evaluated the effect intravenous alfentanil on experimental cutaneous hyperalgesia created using this method. Eighteen subjects participated in a randomized, double-blinded, placebo controlled crossover study consisting of two sessions, one with alfentanil and one with placebo. Using a computer-controlled infusion pump, alfentanil or matching placebo was maintained at a constant plasma level of 75 ng/ml for one 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 non-painful heat created an area of secondary cutaneous hyperalgesia and significant decrease in mechanical pain threshold on heat-treated right

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Attestation: Carolyn Schiffner, M.D. approved the final manuscript and reviewed the original study data and data analysis.

Conflicts of Interest: None

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Attestation: Gery Schulteis, Ph.D. approved the final manuscript and reviewed the original study data and data analysis.

Conflicts of Interest: None

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Contribution: This author contributed to the study design, conduct of the study, data collection, data analysis and manuscript preparation.

Attestation: Mark Wallace, M.D. approved the final manuscript and reviewed the original study data and data analysis. Mark Wallace, M.D. is the archival author.

Conflicts of Interest: None

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Did a Section Editor solicit this submission? No

IRB: University of California San Diego Institutional Review Board. 858 455 5050

versus untreated left during placebo administration. Alfentanil prevented the hypersensitivity when compared to placebo ($p<0.05$), but failed to reduce the area of secondary hyperalgesia created by non-painful heat when compared to placebo ($p=0.06$). 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 non-painful 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

INTRODUCTION

The manifestation of clinical pain involves numerous complex mechanisms, which are difficult to isolate in the clinical setting (e.g. tissue and nerve injury accompanied by inflammation).¹ Furthermore, patients treated for pain often receive multi-drug 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 which 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 alpha-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 using topical capsaicin and heat sensitization, followed by rekindling with a non-painful heat stimulus has been used; however, the pharmacology of this model is very similar to the intradermal capsaicin model.^{10–12}

A model of cutaneous hyperalgesia has been described that uses non-painful 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 non-painful heat.

METHODS

After informed written consent, eighteen healthy volunteers (thirteen male and five female, ages 23–57) participated in a two-session protocol conducted in accordance with the Helsinki Declaration and approved by the IRB 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, 6) lack of ability to understand the experimental protocol and to adequately communicate in English. Nineteen subjects were evaluated for the study, with one subject excluded for bradycardia and heart murmur during the screening physical exam. The volunteers were healthy, ages 18–65, had no history of drug abuse, allergy to alfentanil, nor current painful condition. Each subject underwent two sessions, which were randomized based on a computer-generated randomization schedule, blinded to both the patient and experimenter, and separated by one month.

An experimental protocol for each subject was as follows. On day one, 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 one 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, connected to a computer controlled infusion pump (CCIP), and an intravenous infusion of Lactated Ringers solution at a rate of 50mL/hr was maintained while a plasma concentration of 75ng/mL of alfentanil was reached and maintained by the CCIP 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 non-painful heat stimulus was applied to the dorsal aspect of the right thenar eminence using a focused heat lamp with a lit area of 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. Upon completion of the final sensory tests, the infusion was stopped and the patient was monitored for 1–2 hours before being released. The second visit repeated all of the above-described methods, and occurred at least one month later.

Neurosensory testing was performed i) prior to infusion on dorsal aspects of right and left thenar eminences, ii) following both infusion and heat stimulation of the dorsal aspect of the right thenar eminence in the area of direct heat stimulation, and iii) 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 four measurements as described below: i) warm and cold sensation; ii) warm and cold pain; iii) touch; iv) 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 (VAS). 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) with a thermode applied to the dorsal aspect of the hand. The probe was 2cm × 2cm and had a 1° C/second rate of change for warm and cool sensation and 1.5° C/second 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 (VAS). 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, which 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 endpoint was pain and a VAS 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 five times, at a rate of 1/sec, with a VAS recorded. Pain elicited by foam brush stroking was also measured at baseline.¹⁵

Immediately upon completion of heat lamp stimulation (i.e. 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 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 four 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 (cm²). The neurosensory thresholds were then established at the center of the site of heat stimulation for determination of primary hyperalgesia.

JMP Pro software (SAS Institute) 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 eighteen subjects was initially analyzed as a group, using simple comparison of means for continuous variables such as temperature and areas, and means for non-continuous 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 significantly affected by drug administration, nor heat lamp stimulation. Significance was then established using paired ranking statistics and a p-value <0.05 for all non-continuous variables (all except mapped areas). For continuous variables (mapped areas) ANOVA 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. (Figure 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 ($p < 0.05$) 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)

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 ($p < 0.05$). Mean time to lamp pain for placebo was 48 ± 32 minutes (median with interquartile range was 39 (21–86) and for alfentanil 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 versus 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 ($p = 0.06$ 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 comparing the area of secondary hyperalgesia to heat lamp time, there was no significant correlation in the placebo ($r = -0.23$), alfentanil ($r = -0.15$), nor 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 one report of blister formation at the stimulation site. Side effects of intravenous alfentanil included sedation, light-headedness and nausea. (Figure 4) Two patients received anti-emetic medication for nausea during one of their treatments and two patients experienced episodes of emesis secondary to nausea. All patients were followed up 2 days post treatment, with no patients reporting any significant discomfort at the stimulation site nor any residual nausea, vomiting, or other problems post treatment.

DISCUSSION

The induction of an area of secondary hyperalgesia with non-painful heat constitutes a safe and reliable method of inducing cutaneous experimental hypersensitivity and pain in healthy volunteers. In a previous study, the ability of non-painful heat to induce an area of hyperalgesia was demonstrated¹³, but the ability of an opiate to alter this area has not previously been studied. The purpose of this study was two-fold: 1) to induce an area of hyperalgesia using non-painful 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 (CMH) since 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, non-noxious heat results in pain (heat hyperalgesia mediated by CMH) and painful heat results in exaggerated reports of pain (heat hyperalgesia mediated by both CMH and AMH).^{16,19,20} In contrast, after thermal injury to glabrous 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 model²² 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 UV-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}, NSAIDs³¹, and COX-2 inhibitors,³² whereas 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 UV-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 since we used temperatures that were not high enough to activate these fibers.

As expected, this model of non-painful 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 studies using intradermal capsaicin. It is difficult to make comparisons on the area of hyperalgesia of the non-painful heat model with the topical capsaicin models since the area of capsaicin applied to the skin is much larger than the area stimulated by the heat used in this model. The smaller area 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 pharmacogenomics 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 inter-individual differences.³⁶ We did not determine if the non-painful heat stimulus would have resulted in secondary hyperalgesia and allodynia since we only measured this after the subjects' first

report of pain. Although, this report of pain was much lower than what is observed with capsaicin models.

Intradermal capsaicin results in a zone of primary hyperalgesia 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 non-painful heat model used in this study resulted in a decrease in mechanical pain but not thermal pain thresholds which suggests that the non-painful 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 non-painful 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 A-delta 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 capsaicin⁶ 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 (non-painful) thresholds, this was not reversed by alfentanil. This is consistent with the specific effects of an opioid on C-fiber activity. Mechanical non-painful stimuli are mediated by A-beta 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 comparing the area of secondary hyperalgesia to heat lamp time, there is no significant correlation in the placebo ($r=-0.23$), alfentanil ($r=-0.15$), nor 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 since 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. (Wallace et al, unpublished observations). We used both males and females in our study which could confound the results given then 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 nociceptors result in the generation of areas of primary and secondary hyperalgesia. Duration of these areas have been shown to be dependent upon the initial injury as well as ongoing nociceptor 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 non-painful heat which 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.

Acknowledgments

Funding: This project was supported by Award Number T35H1007491 from the National Institute of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

References

1. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009; 139(2):267–284. [PubMed: 19837031]
2. Dworkin RH, Panarites CJ, Armstrong EP, Malone DC, Pham SV. Healthcare utilization in people with postherpetic neuralgia and painful diabetic peripheral neuropathy. *Journal of the American Geriatrics Society*. 2011; 59(5):827–836. [PubMed: 21568954]
3. Gilron I, Baron R, Jensen T. Neuropathic pain: principles of diagnosis and treatment. *Mayo Clinic proceedings*. 2015; 90(4):532–545. [PubMed: 25841257]
4. Reimer M, Helfert SM, Baron R. Phenotyping neuropathic pain patients: implications for individual therapy and clinical trials. *Curr Opin Support Palliat Care*. 2014; 8(2):124–129. [PubMed: 24670811]
5. Olesen AE, Andresen T, Staahl C, Drewes AM. Human experimental pain models for assessing the therapeutic efficacy of analgesic drugs. *Pharmacological reviews*. 2012; 64(3):722–779. [PubMed: 22722894]
6. Wallace MS, Rowbotham MC, Katz NP, et al. A randomized, double-blind, placebo-controlled trial of a glycine antagonist in neuropathic pain. *Neurology*. 2002; 59(11):1694–1700. [PubMed: 12473754]
7. Wallace MS, Barger D, Schulteis G. The effect of chronic oral desipramine on capsaicin-induced allodynia and hyperalgesia: a double-blinded, placebo-controlled, crossover study. *Anesthesia and analgesia*. 2002; 95(4):973–978. table of contents. [PubMed: 12351279]
8. Eisenach JC, Hood DD, Curry R, Tong C. Alfentanil, but not amitriptyline, reduces pain, hyperalgesia, and allodynia from intradermal injection of capsaicin in humans. *Anesthesiology*. 1997; 86(6):1279–1287. [PubMed: 9197296]
9. Wallace MS, Ridgeway B 3rd, Leung A, Schulteis G, Yaksh TL. Concentration-effect relationships for intravenous alfentanil and ketamine infusions in human volunteers: effects on acute thresholds and capsaicin-evoked hyperpathia. *J Clin Pharmacol*. 2002; 42(1):70–80. [PubMed: 11808827]

10. Dirks J, Fabricius P, Petersen KL, Rowbotham MC, Dahl JB. The effect of systemic lidocaine on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers. *Anesthesia and analgesia*. 2000; 91(4):967–972. [PubMed: 11004058]
11. Petersen KL, Jones B, Segredo V, Dahl JB, Rowbotham MC. Effect of remifentanyl on pain and secondary hyperalgesia associated with the heat–capsaicin sensitization model in healthy volunteers. *Anesthesiology*. 2001; 94(1):15–20. [PubMed: 11135717]
12. Petersen KL, Maloney A, Hoke F, Dahl JB, Rowbotham MC. A randomized study of the effect of oral lamotrigine and hydromorphone on pain and hyperalgesia following heat/capsaicin sensitization. *The journal of pain: official journal of the American Pain Society*. 2003; 4(7):400–406. [PubMed: 14622682]
13. Cervero F, Gilbert R, Hammond RG, Tanner J. Development of secondary hyperalgesia following non-painful thermal stimulation of the skin: a psychophysical study in man. *Pain*. 1993; 54(2): 181–189. [PubMed: 8233532]
14. Maier C, Baron R, Tolle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain*. 2010; 150(3):439–450. [PubMed: 20627413]
15. Walk D, Sehgal N, Moeller-Bertram T, et al. Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. *The Clinical journal of pain*. 2009; 25(7):632–640. [PubMed: 19692806]
16. LaMotte RH, Thalhammer JG, Torebjork HE. Peripheral neural mechanisms of cutaneous hyperalgesia following mild injury by heat. *J Neurosci*. 1982; 2:765–781.
17. Thalhammer JG, LaMotte RH. Spatial properties of nociceptor sensitization following heat injury of the skin. *Brain research*. 1982; 231(2):257–265. [PubMed: 7055680]
18. Campbell JN, Khan AA, Meyer RA, Raja SN. Responses to heat of C-fiber nociceptors in monkey are altered by injury in the receptive field but not by adjacent injury. *Pain*. 1988; 32(3):327–332. [PubMed: 3362567]
19. Brennum J, Dahl JB, Moiniche S, Arendt-Nielsen L. Quantitative sensory examination of epidural anaesthesia and analgesia in man: effects of pre- and post-traumatic morphine on hyperalgesia. *Pain*. 1994; 59(2):261–271. [PubMed: 7892024]
20. Jensen, TS., Brennum, J. The relation of thermally and mechanically evoked pain to pathological pain. In: Hansson, P., Lindholm, U., editors. *Touch, Temperature, and Pain in Health and Disease: Mechanisms and Assessments*. Seattle: IASP Press; 1994. p. 373-388.
21. Handwerker, HO., Reeh, PW. Pain and Inflammation. In: Bond, MR, Charlton, JR., Woolf, CJ., editors. *Proceedings of the VIth World Congress on Pain*. Amsterdam: IASP Press; 1991. p. 59-70.
22. Ilkjaer S, Petersen KL, Brennum J, Wernberg M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans. *British journal of anaesthesia*. 1996; 76(6):829–834. [PubMed: 8679358]
23. Petersen KL, Brennum J, Dahl JB. Experimental evaluation of the analgesic effect of ibuprofen on primary and secondary hyperalgesia. *Pain*. 1997; 70(2–3):167–174. [PubMed: 9150290]
24. Werner MU, Perkins FM, Holte K, P JL, Kehlet H. Effects of gabapentin in acute inflammatory pain in humans. *Regional anesthesia and pain medicine*. 2001; 26:322–328. [PubMed: 11464350]
25. Sjolund KF, Segerdahl M, Sollevi A. Adenosine reduces secondary hyperalgesia in two human models of cutaneous inflammatory pain. *Anesthesia and analgesia*. 1999; 88(3):605–610. [PubMed: 10072015]
26. Warncke T, Stubhaug A, Jorum E. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. *Pain*. 1997; 72(1–2):99–106. [PubMed: 9272793]
27. Schulte H, Sollevi A, Segerdahl M. Dose-dependent effects of morphine on experimentally induced cutaneous pain in healthy volunteers. *Pain*. 2005; 116(3):366–374. [PubMed: 15982813]
28. Gustorff B, Anzenhofer S, Sycha T, Lehr S, Kress HG. The sunburn pain model: the stability of primary and secondary hyperalgesia over 10 hours in a crossover setting. *Anesthesia and analgesia*. 2004; 98(1):173–177. table of contents. [PubMed: 14693614]

29. Koppert W, Likar R, Geisslinger G, Zeck S, Schmelz M, Sittl R. Peripheral antihyperalgesic effect of morphine to heat, but not mechanical, stimulation in healthy volunteers after ultraviolet-B irradiation. *Anesthesia and analgesia*. 1999; 88(1):117–122. [PubMed: 9895077]
30. Gustorff B, Hoeckl K, Sycha T, Felouzis E, Lehr S, Kress HG. The effects of remifentanyl and gabapentin on hyperalgesia in a new extended inflammatory skin pain model in healthy volunteers. *Anesthesia and analgesia*. 2004; 98(2):401–407. table of contents. [PubMed: 14742378]
31. Bickel A, Dorfs S, Schmelz M, Forster C, Uhl W, Handwerker HO. Effects of antihyperalgesic drugs on experimentally induced hyperalgesia in man. *Pain*. 1998; 76(3):317–325. [PubMed: 9718250]
32. Sycha T, Anzenhofer S, Lehr S, et al. Rofecoxib attenuates both primary and secondary inflammatory hyperalgesia: a randomized, double blinded, placebo controlled crossover trial in the UV-B pain model. *Pain*. 2005; 113(3):316–322. [PubMed: 15661439]
33. LaMotte RH, Lundberg LE, Torebjork HE. Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *The Journal of physiology*. 1992; 448:749–764. [PubMed: 1593488]
34. LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *Journal of neurophysiology*. 1991; 66(1):190–211. [PubMed: 1919666]
35. Chakour MC, Gibson SJ, Bradbeer M, Helme RD. The effect of age on A delta- and C-fibre thermal pain perception. *Pain*. 1996; 64(1):143–152. [PubMed: 8867257]
36. Orlova IA, Alexander GM, Qureshi RA, et al. MicroRNA modulation in complex regional pain syndrome. *J Transl Med*. 2011; 9:195. [PubMed: 22074333]
37. Torebjork HE, Lundberg LE, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *The Journal of physiology*. 1992; 448:765–780. [PubMed: 1593489]
38. Culp WJ, Ochoa J, Cline M, Dotson R. Heat and mechanical hyperalgesia induced by capsaicin. Cross modality threshold modulation in human C nociceptors. *Brain: a journal of neurology*. 1989; 112(Pt 5):1317–1331. [PubMed: 2804614]
39. Simone DA, Baumann TK, LaMotte RH. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. *Pain*. 1989; 38(1):99–107. [PubMed: 2780068]
40. Simone DA, Ngeow JY, Putterman GJ, LaMotte RH. Hyperalgesia to heat after intradermal injection of capsaicin. *Brain research*. 1987; 418(1):201–203. [PubMed: 3664271]
41. Meyer RA, Campbell JN. Myelinated nociceptive afferents account for the hyperalgesia that follows a burn to the hand. *Science*. 1981; 213(4515):1527–1529. [PubMed: 7280675]
42. Wang CY. Respiratory depression after extradural fentanyl. *British journal of anaesthesia*. 1992; 69(5):544.
43. Omote K, Kitahata LM, Collins JG, Nakatani K, Nakagawa I. Interaction between opiate subtype and alpha-2 adrenergic agonists in suppression of noxiously evoked activity of WDR neurons in the spinal dorsal horn. *Anesthesiology*. 1991; 74(4):737–743. [PubMed: 1672579]
44. Fillingim RB, Gear RW. Sex differences in opioid analgesia: clinical and experimental findings. *European journal of pain*. 2004; 8(5):413–425. [PubMed: 15324773]

Figure 1.

A: The effect of a non-painful heat stimulus on mechanical sensation. The application of a non-painful 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) versus non-treated left (B) during placebo administration. These heat lamp effects were not abolished by the administration of alfentanil. N=18 in each group.

B: The effect of a non-painful heat stimulus on mechanical sensation. The application of a non-painful 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) versus non-treated right (B) during placebo administration. These heat lamp effects were not abolished by the administration of alfentanil. N=18 in each group.

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Figure 2.

A: The effect of a non-painful heat stimulus on mechanical pain. The application of a non-painful 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) versus non-treated left

(B) during placebo administration. These heat lamp effects were abolished by the administration of alfentanil. N=18 in each group.

B: The effect of a non-painful heat stimulus on mechanical pain. The application of a non-painful 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) versus non-treated right (B) during placebo administration. These heat lamp effects were abolished by the administration of alfentanil. N=18 in each group

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Figure 3. The effect of alfentanil on non-painful 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 ($p = 0.06$). $N=18$ 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.

Table 1

Summary of Sensory Thresholds. Values are means +/- standard deviations

	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)