

Effect of Remifentanil on Pain and Secondary Hyperalgesia Associated with the Heat–Capsaicin Sensitization Model in Healthy Volunteers

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Background: **The heat–capsaicin sensitization model was developed as a noninvasive and noninjurious human experimental pain model. The sequential application of moderate intensity thermal and topical chemical stimuli produces stable and long-lasting areas of cutaneous secondary hyperalgesia. The aim of the present study was to validate the heat–capsaicin sensitization model as a tool for testing analgesic drug efficacy. Responsivity of model-associated measures was tested with remifentanil, a potent and ultrashort acting μ-opioid agonist.**

Methods: **Sensitization was induced by heating forearm skin with a thermode at 45°C for 5 min, immediately followed by application of 0.075% capsaicin cream for 30 min. Sensitization was rekindled four times at 40-min intervals with the thermode at 40°C for 5 min. After each rekindling, areas of secondary hyperalgesia were measured, and the painfulness of thermal stimulation in normal skin with 45°C for 1 min (long thermal stimulation [LTS]) was rated. Before and during the second rekindling, remifentanil 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or saline–placebo was infused for 35 min.**

Results: **Infusion of remifentanil reduced the areas of secondary hyperalgesia to 29–30% of baseline size compared with 75–83% during placebo. Similarly, remifentanil reduced the painfulness of LTS to 29% of baseline severity compared with 84% during placebo. Areas of secondary hyperalgesia and LTS painfulness returned to baseline levels by the time of the third rekindling, demonstrating rapid disappearance of remifentanil analgesia and possibly transient spontaneous opioid withdrawal hyperalgesia.**

Conclusion: **Using the heat–capsaicin sensitization model, opioid analgesia and suppression of secondary hyperalgesia was reliably demonstrated without skin injury.**

HUMAN experimental pain models can play an important role in the study of pain mechanisms and in the testing of new analgesic drugs.[1–3] The current path of testing new analgesic drugs moves from studies of animal experimental pain models to pharmacokinetics–tolerability studies in healthy volunteers. Costly clinical trials in pain patients are then initiated without proof that the drug to be tested has analgesic activity in humans. Using human experimental pain models, new drugs could be tested rapidly and efficiently in healthy volunteers for analgesic potency and side effects profile under randomized, double-blind conditions. Limitations of the existing human experimental pain models lead to the development of the heat–capsaicin sensitization model.[4]

As originally described in normal human subjects by Lewis,[5] prolonged or intense focal noxious stimulation produces reversible cutaneous sensory changes. Such stimuli produce a zone of primary hyperalgesia, comprising the stimulated area and characterized by lowered pain thresholds (allodynia) to thermal and mechanical stimulation and an enhanced response to suprathreshold stimulation (hyperalgesia). Neurophysiologic studies in humans have demonstrated that primary hyperalgesia is caused in part by sensitization of primary afferent nociceptors.[6] In a zone around the area of primary hyperalgesia (where no stimulation was performed), secondary hyperalgesia is present. In this area there is dynamic mechanical allodynia[7–9] transmitted *via* Aß fibers[10–12] and tactile hyperalgesia probably transmitted *via* Aδ or C fibers. In animals, the receptive field of spinal cord dorsal horn neurons enlarges, and their response to Aß-mechanoreceptor stimulation increases after intense noxious stimulation.[13] Hence, secondary hyperalgesia is believed to be caused mainly by sensitization of central pain transmission neurons.

An ideal human experimental pain model would induce stable and long-lasting sensory changes without tissue injury. Because the duration and the extent of the secondary hyperalgesia area depend on the intensity of the initial stimulus applied to the primary zone, previous models that have produced long-lasting secondary hyperalgesia have also had the potential for skin injury or have been invasive. Stimulation at 45°C for 3 min produces secondary hyperalgesia lasting no more than a few minutes after termination of the heat stimulus.[14] As used in the burn-injury model, stimulation at 47°C for 7 min produces stable and long-lasting primary and secondary hyperalgesia.[9,14–16] However, a definite skin injury with blistering or skin pigmentation changes occurs in up to 25% of young healthy male volunteers.[15,16] Models using

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capsaicin can produce pain and primary and secondary hyperalgesia. Sensory changes after low-strength (0.1%) topical capsaicin are minimal, and with a higher concentration (1%), sensory changes are more pronounced but still brief.[12,17,18] Intradermal injection of capsaicin results in rapid-onset intense pain and long-lasting secondary hyperalgesia.[8,19–21]

The recently developed heat–capsaicin sensitization model noninvasively combines lower levels of thermal and chemical stimulation to produce long-lasting cutaneous hyperalgesia without obvious cutaneous injury.[4] By periodically heating the zone of primary hyperalgesia to a previously nonpainful temperature of 40°C, stable areas of secondary hyperalgesia can be maintained for at least 4 h. The aim of the present study was to validate the heat–capsaicin sensitization model as a tool in testing analgesic drug efficacy. The potent high efficacy μ-opioid receptor agonist remifentanil was used as a positive control because opioids have been demonstrated to suppress both clinical and experimental pain.[3] Remifentanil has no significant effect at other types of opioid receptors and is metabolized rapidly to an inactive metabolite by nonspecific plasma esterases with a systemic half-life of 9–11 min and a "context-sensitive" half-life time (the time to a 50% decrease of the effective site concentration) of approximately 3–4 min.[22–24]

Materials and Methods

Subjects

Subjects were paid healthy male and female volunteers. All were free of pain, medication, and caffeine at the time of testing and had no history of opioid use. After providing informed written consent, subjects underwent a separate orientation session to familiarize them with the heat–capsaicin sensitization method, sensory testing, and pain ratings. During the two infusion sessions, 1 week apart, subjects received infusions of saline or remifentanil in random order under double-blind conditions. The study was conducted in accordance with the Declaration of Helsinki and was approved by both the Committee on Human Research at the University of California–San Francisco and the California Research Advisory Panel.

Pain and Hyperalgesia Assessment

Pain during thermal stimulation was rated continuously on a computerized visual analog scale (VAS). The VAS was anchored with the descriptors "no pain" and "worst pain imaginable." Pain during capsaicin stimulation was rated at 5-min intervals on a 100-mm pen-and-paper VAS, anchored by the same descriptors.

The area of secondary hyperalgesia was quantified with a foam paintbrush and a 20.9-g von Frey hair (a mildly noxious pinlike sensation) by stimulating along four linear paths arranged vertically and horizontally around the stimulation site in 5-mm steps at 1-s intervals. Stimulation along each path started well outside the hyperalgesic area and continued toward the treated skin area until subjects reported a definite change in sensation (burning, tenderness, more intense pricking). The border was marked on the skin with a felt pen, and the rostral–caudal and lateral–medial distances were measured for surface area calculations.

Heat Stimulation

Thermal stimulation was conducted using the Medoc TSA 2001 (Medoc, Minneapolis, MN). The 15.7-cm^2 surface area thermode is a computer-controlled Peltier device that warms the skin surface at a linear rate from a probe holding temperature of 32°C to a safety cutoff of 50°C. Before sensitization, the heat pain detection threshold (HPDT) was determined four times in a site in nontreated skin on the nondominant forearm. HPDT was defined as the median of the four determinations and was measured five times throughout the study day. Another stimulus location was marked in nontreated skin on the nondominant upper arm, and in this site subjects were asked to rate the painfulness of a 1-min 45°C heat stimulus (long thermal stimulation [LTS]) on the electronic VAS five times throughout the study day.

Heat–Capsaicin Sensitization

The treatment site was marked with a felt pen on the dominant forearm (22.8 cm^2). Sensitization was produced by heating the skin of the forearm to 45°C for 5 min with the thermode. During heat stimulation, pain was rated continuously on the electronic VAS. After heat stimulation, the area of secondary hyperalgesia to brush and von Frey hair stimulation was mapped. Immediately thereafter, the skin was covered with capsaicin cream (0.075% Capsaicin; Clay-Park Labs Inc., New York, New York) for 30 min. After capsaicin removal, the area of secondary hyperalgesia was mapped again. The sensitization was rekindled four times at 40-min intervals throughout the study day by heating the treatment site with the thermode at 40°C for 5 min. The first rekindling was performed 80 min after initial heat sensitization, and the last rekindling was performed at 200 min after initial sensitization. Mapping of secondary hyperalgesia areas was performed after each rekindling.

Study Drug Infusion Sessions

The timing of the procedures is summarized in figure 1. Infusions were performed and monitored by the authors (B. J. or V. S.). The remifentanil and saline placebo solutions were prepared in coded infusion syringes by a physician not involved in the study. At the beginning of the infusion session, an intravenous catheter was placed on the dorsal side of the nondominant hand and was kept open with saline. The heat–capsaicin sensitization

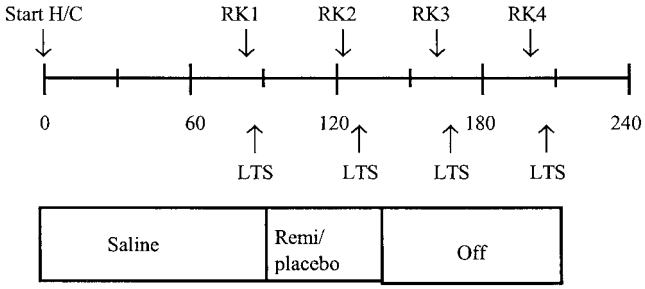

Fig. 1. Time course in minutes of infusion sessions. H/C = heat–capsaicin sensitization; RK = rekindling (40°C for 5 min); LTS = long thermal stimulation (45°C for 1 min); Remi/placebo = infusion with remifentanil or placebo. See text for infusion rates.

was established. Immediately after the first rekindling cycle, baseline areas of secondary hyperalgesia to brush and von Frey hair stimulation were determined along with baseline HPDT and ratings of the painfulness of LTS. The infusion was then started. The study drug was administered by an electronic pump (Baxter AS48 syringe pump; Baxter Healthcare, Deerfield, IL) as a slow intravenous infusion beginning at 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil (or equivalent volume of saline). After 5 min, the infusion rate of remifentanil was increased to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and maintained at this level for an additional 35 min before the infusion was stopped. If the respiration rate decreased to less than 6 breaths/min, the infusion rate was reduced to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. During the infusion, heart rate and rhythm, blood pressure, respiration rate, and oxygen saturation were monitored continuously. Oxygen was administered *via* a nasal catheter (2 l/min) during the entire infusion time. A 6-item side-effect checklist (nausea, itching, dry mouth, sleepy, light-headed, spacey) was completed by the anesthesiologist every 5 min using a 0–3 numerical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The second rekindling cycle was performed after 25-min steady state infusion at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and immediately thereafter, the areas of secondary hyperalgesia to brush and von Frey hair stimulation were determined along with HPDT and painfulness of LTS. The infusion was then turned off. A third and fourth rekindling cycle was performed after the infusion was terminated (30 and 70 min after infusion), and after these rekindling cycles, the area of secondary hyperalgesia, HPDT, and painfulness of LTS were determined.

Statistical Analysis

Data are presented as mean values ± SD. Painfulness of the initial heating (45°C for 5 min) and LTS are calculated as area under the curve converted to VAS values on a 0–100 scale and reported as mean VAS values over the stimulation period. The primary outcome measures (area of secondary hyperalgesia to brush and von Frey hair stimulation and painfulness of LTS) are each expressed as a percentage of baseline values (preinfusion) and were analyzed using paired *t* tests. The Wilcoxon signed rank test was used to analyze changes in HPDT as these could be positive or negative. A *P* value of 0.05 was considered statistically significant.

Results

Sixteen subjects were enrolled, and the 14 (9 men, 5 women; mean age, 34 yr [range, 22–56 yr]) who completed both infusion sessions are included in the data analysis. Two subjects receiving remifentanil in their first session did not complete the study; one cited family reasons, and one withdrew consent.

Heat–Capsaicin Sensitization

In all 14 subjects, initial sensitization from heat stimulation with 45°C for 5 min produced an area of secondary hyperalgesia to brush and von Frey hair stimulation (brush: 71 ± 39 cm^2; von Frey hair: 90 ± 55 cm^2; mean of study days 1 and 2 ± SD). The areas expanded after 30-min application of 0.075% topical capsaicin (brush: 124 ± 60 cm^2; von Frey hair: 142 ± 65 cm^2). After the first rekindling cycle (preinfusion baseline), the areas were 112 ± 48 cm^2 (brush) and 128 ± 63 cm^2 (von Frey hair). The baseline areas of secondary hyperalgesia to brush stimulation were slightly smaller on the remifentanil day (103 ± 46 cm^2) than on the placebo day (122 ± 54 cm^2; $P = 0.03$), but the baseline areas of secondary hyperalgesia to von Frey hair stimulation (remifentanil: 125 ± 59 cm^2; placebo: 132 ± 71 cm^2) and other pain measures did not differ between the two infusion days. The average painfulness of the initial heat stimulation (45°C for 5 min) was 32 ± 17 on the electronic VAS. The maximal pain ratings during the 30-min capsaicin stimulation was 37 ± 24 on the 100-mm pen-and-paper VAS, which was reached between 20 and 30 min of stimulation. All subjects developed skin redness and flare. The flare lasted for up to 2 h, and the redness persisted for up to 12 h. Beyond that, no skin changes were observed.

Effects of Remifentanil

During the infusion of remifentanil, the area of secondary hyperalgesia to brush stimulation was reduced to 29% of baseline size (28 ± 9 cm^2) compared with 75% of baseline (92 ± 53 cm^2) during infusion of placebo ($P = 0.0002$; fig. 2A). A similar reduction was observed in the area of secondary hyperalgesia to von Frey hair stimulation. During remifentanil infusion the area was 30% of baseline (34 ± 17 cm^2), whereas during placebo the area was 83% of baseline (106 ± 54 cm^2; $P < 0.0001$; fig. 2B). After termination of the infusion, as measured after the third rekindle, the area of secondary hyperalgesia to brush was 75% ± 27% of baseline size on the placebo

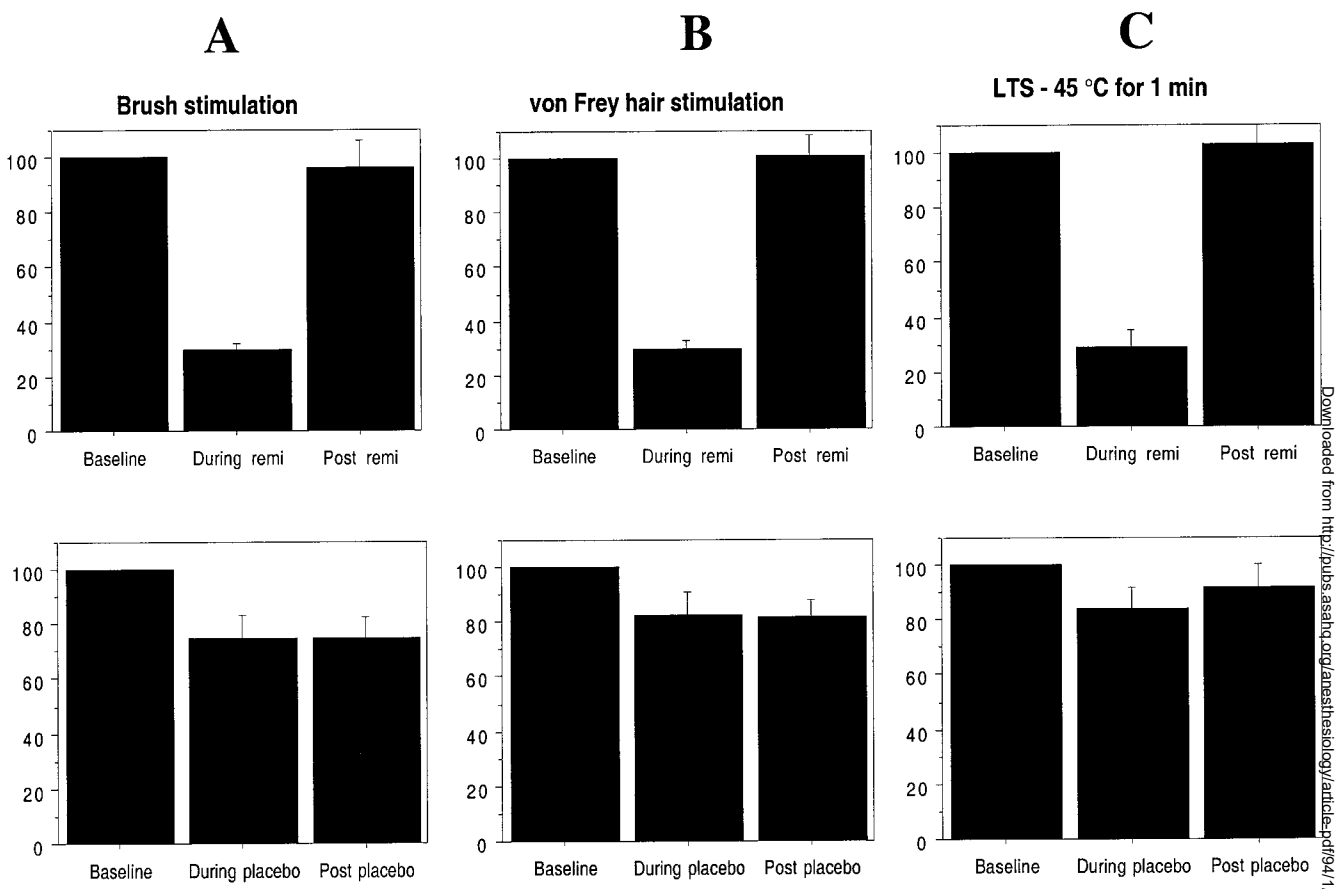

Fig. 2. Area of secondary hyperalgesia in percentage of baseline to brush stimulation (*A*) and von Frey hair stimulation (*B*). Baseline = area of secondary hyperalgesia after the first rekindle (before infusion); during infusion = area of secondary hyperalgesia after the second rekindle (25-min steady state infusion at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$); postinfusion = area of secondary hyperalgesia after the third rekindle (30 min after infusion was terminated). (*C*) Painfulness of long thermal stimulation (LTS; 45°C for 1 min) in percentage of baseline. Baseline = painfulness of LTS before infusion; during infusion = painfulness of LTS (25-min steady state infusion at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Postinfusion = painfulness of LTS 30 min after infusion was terminated.

day, whereas on the remifentanil day the area returned to 96% ± 39% of baseline size ($P = 0.11$). Likewise, the area of secondary hyperalgesia to von Frey hair stimulation was 82% ± 23% of baseline size on the placebo day but returned to 101% ± 29% on the remifentanil day ($P = 0.06$).

Before study drug infusion, the mean painfulness of LTS (45°C for 1 min) was 28 ± 12 on the electronic VAS. During remifentanil infusion, the mean painfulness of LTS was reduced to 8 ± 8 on the 0–100 VAS scale compared with 22 ± 14 during the placebo infusion, equivalent to 29% of baseline during remifentanil compared with 84% of baseline during the placebo infusion ($P = 0.0003$; fig. 2C). After the remifentanil infusion was terminated, the painfulness of LTS exceeded baseline levels (103% of baseline), whereas on the placebo day, the painfulness was rated as 92% of baseline ($P = 0.43$).

The HPDT in normal skin increased 2°C during the remifentanil infusion compared with baseline (baseline: 42.4 ± 1.9°C; during infusion: 44.4 ± 1.5°C). During the placebo infusion, HPDT increased only 0.6°C compared with baseline (baseline: 42.3 ± 1.8°C; during infusion: 42.8 ± 1.9°C). This difference between the infusion days was significant ($P = 0.01$, Wilcoxon signed rank test). After the infusion was turned off, the HPDT decreased to 41.6 ± 2.4°C on the remifentanil day and to 42.3 ± 1.9°C on the placebo day ($P = 0.43$).

Physiologic Measures during Drug Infusion

The mean total dose of remifentanil was 242.4 ± 36 μg. In all subjects, the remifentanil infusion rate was increased to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after 5 min of infusion at 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In one subject, the respiration rate decreased to 4 breaths/min after 10-min infusion with 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ but without oxygen desaturation. The infusion rate was decreased to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remainder of the infusion period, and the respiration rate immediately normalized. All subjects maintained oxygen saturation above 97%. Blood pressure and heart rate stayed within normal physiologic limits.

Table 1. Side Effect Ratings during Remifentanil Infusion

Symptom	Remifentanil	Placebo	*P*
Nausea	0.1	0	NS
Itching	1.6	0.1	0.001
Dry mouth	1.4	0	0.002
Sleepy	1.7	0.4	0.005
Light-headed	1.7	0.1	0.002
"Spacey"	2.0	0.2	0.002

Six-item side-effect checklist completed every 5 min using a 0–3 numerical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Table of group mean of subjects' highest ratings during the 40 min infusion, n = 14.

Side Effects

The side effects (highest ratings during the infusion) are listed in table 1. Side effects were more severe during the remifentanil infusion than during placebo ($P < 0.005$). Most prominent were descriptions of feeling "spacey" and "itching." No subject requested early termination of the infusion because of side effects, and the side effects were not severe enough to impair the subject's ability to cooperate with the sensory testing performed during infusion. One subject reported chills and goose flesh during the postinfusion period. No other subject reported opioid withdrawal-like symptoms. In all subjects, side effects disappeared 10 min after the infusion was terminated.

Discussion

As in our previous study, the heat–capsaicin sensitization procedure induced stable, quantifiable, long-lasting, secondary hyperalgesia without tissue injury.[4] Secondary hyperalgesia to brush and von Frey hair stimulation was reliably and profoundly suppressed during infusion of remifentanil compared with placebo, demonstrating analgesic responsiveness of the heat–capsaicin sensitization model. The areas of secondary hyperalgesia had returned to baseline levels by the next measurement, 30 min after the remifentanil infusion had been stopped. The rapid return to preinfusion levels of the areas of secondary hyperalgesia demonstrates that the underlying sensitization is able to persist through a brief period of intense suppression by the potent opioid remifentanil.

To our knowledge, the analgesic effect of remifentanil on cutaneous secondary hyperalgesia has not previously been investigated. It has been demonstrated that painfulness of capsaicin injection and the area of secondary hyperalgesia to pin-prick stimulation was reduced during infusion of high-dose alfentanil (a longer-acting μ-opioid agonist).[20,21,25] Administering a single intravenous bolus dose of morphine (0.15 mg/kg), Warncke *et al.*[26] failed to demonstrate an analgesic effect on the area of secondary hyperalgesia after experimental burn injury. In two of the studies, it was difficult to analyze opioid effects on secondary hyperalgesia to gentle mechanical stimuli because the area either did not develop after capsaicin injection or rapidly disappeared.[20,21]

In the present study, infusion of remifentanil reduced the painfulness of LTS and increased the HPDTs. In humans, a dose-dependent reduction of painfulness of acute noxious stimulation with intravenous administration of morphine, alfentanil, fentanyl, and hydromorphone has been demonstrated.[3,27–29] In addition, a dose-dependent reduction in pain intensity and "bothersomeness" of cold-pressor testing during remifentanil infusion has been demonstrated.[30,31] Single-dose studies of intravenous opioids (0.1–0.15 mg/kg) have been less consistent; ischemic pain was reduced[32] but not laser warmth and pin-prick thresholds[33] and HPDTs.[26]

Remifentanil analgesia disappeared rapidly, as evidenced by the return to preinfusion values for secondary hyperalgesia areas, painfulness of LTS, and the HPDT. In fact, there is evidence to suggest transient withdrawal hyperalgesia was present 30 min after infusion. While the areas of secondary hyperalgesia remained at 75–82% of baseline size after the placebo infusion had been turned off, the areas returned to 96–101% of baseline size after the remifentanil infusion was turned off. The time course of the cutaneous hyperalgesia on the placebo day are similar to those observed in the earlier methodology study. Furthermore, the painfulness of LTS and HPDTs after remifentanil infusion are also consistent with withdrawal hyperalgesia, albeit not statistically significant. It has been shown in animal studies that during both precipitated and nonprecipitated opioid withdrawal, animals develop hyperalgesia to acute noxious thermal stimulation.[34,35] It is possible that with the ultrashort half-life of remifentanil, the first postinfusion measurement cycle was already past the peak period of withdrawal hyperalgesia. Spontaneous complaints of withdrawal-like symptoms after remifentanil infusion occurred in one subject and lasted only 10 min.

The subjects consistently reported a higher side-effect score during the remifentanil infusion than during placebo. This may have led to unintentional unblinding of both subjects and investigators. However, we believe that unblinding alone cannot account for the potent opioid analgesic effects observed on every pain-related outcome measure. In a previous study of opioid effects on chronic pain, patients given intravenous benzodiazepines in doses sufficient to match opioid-induced sedation did not experience pain relief.[36]

The heat–capsaicin sensitization model of human experimental pain uses temporary noxious stimulation in a normally functioning pain transmission system to induce temporary peripheral and central sensitization. Chronic sensitization of central pain transmission neurons has been suggested as an important underlying mechanism in chronic pain syndromes.[37–39] In a recent clinical study of patients with postherpetic neuralgia, we used a topical capsaicin challenge to provide indirect evidence of

central nervous system sensitization in the form of chronic secondary hyperalgesia as an underlying pain mechanism in some patients.[40] Moreover, pain and touch-evoked allodynia in postherpetic neuralgia is reduced by opioids.[41] As studies in healthy volunteers are more simple, safer, and can be performed more rapidly than clinical trials in chronic pain patients, the present study supports using human experimental pain models to test new analgesic drugs.

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