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## ***Alfentanil, but Not Amitriptyline, Reduces Pain, Hyperalgesia, and Allodynia from Intradermal Injection of Capsaicin in Humans***

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**Background:** Intradermal injection of capsaicin produces brief pain followed by hyperalgesia and allodynia in humans, and the latter effects are mediated by spinal N-methyl-D-aspartate mechanisms. Amitriptyline recently was shown to antagonize N-methyl-D-aspartate receptors, and in this study, the authors sought to determine the effect of amitriptyline alone and with the opioid alfentanil on hyperalgesia and allodynia produced by intradermal injection of capsaicin.

**Methods:** Forty-six healthy volunteers in the general clinical research center received repeated intradermal injections of capsaicin (100  $\mu$ g) alone or before and after systemic injection of 4 mg midazolam, 25 mg amitriptyline, alfentanil by computer-controlled infusion, or amitriptyline plus alfentanil. Acute pain and areas of mechanical hyperalgesia and allodynia were determined at specified intervals. Blood was obtained for alfentanil and amitriptyline assay.

**Results:** Capsaicin injection produced acute pain followed by hyperalgesia and allodynia. Alfentanil reduced these pain responses in a plasma-concentration-dependent manner, and reduction in hyperalgesia and allodynia correlated with reduction in acute pain. Amitriptyline alone had no effect and did not potentiate alfentanil. Alfentanil produced concentration-dependent nausea, an effect diminished by amitriptyline.

**Discussion:** These data correspond with previous studies in volunteers demonstrating reduction in hyperalgesia and allodynia after intradermal injection of capsaicin by systemically administered opioids, and they suggest that this reduction may be secondary to reduced nociceptive input by acute analgesia. These data do not support the use of acute systemic administration of amitriptyline for acute pain, hyperalgesia, and allodynia, although the roles of chronic treatment and spinal administration are being investigated. (Key words: Ami-

triptyline. Analgesia. Capsaicin. Hyperalgesia. Opioid agonists. Alfentanil. Pain, neuropathic.)

MOST pain can be classified according to its three components. Acute noxious stimuli result in well-localized pain. A more sustained noxious stimulus may result in more diffuse pain and generation of increased pain perception from a painful stimulus (hyperalgesia) and pain from a stimulus previously perceived as innocuous (allodynia). Nerve injury may result in chronic pain, hyperalgesia, and allodynia in a dermatomal or peripheral nerve territory. Recent research has focused on the latter components of pain, because these may play important roles in postsurgical pain and in difficult-to-manage chronic pain syndromes.

Intradermal injection of capsaicin results in acute burning pain that is dose-dependent and brief after doses of 100  $\mu$ g or less, followed by development of hyperalgesia and allodynia to mechanical stimuli that lasts several hours.<sup>1</sup> Development of hyperalgesia and allodynia can be prevented by peripheral nerve block to prevent perception of the acute pain of injection.<sup>2</sup> Animal studies suggest that hyperalgesia and allodynia after intradermal capsaicin injection is mediated *via* stimulation of N-methyl-D-aspartate (NMDA) and other excitatory receptors in the spinal cord, leading to the development of hypersensitivity of dorsal horn neurons to afferent input.<sup>3,4</sup> Thus, this simple model shares many characteristics of animal models of inflammatory pain and has been used experimentally in humans to examine the pharmacology of spinal hypersensitivity.

Systemic administration of the NMDA antagonist ketamine or the opioid alfentanil has been shown to reduce ongoing pain from intradermal injection of a large dose (250  $\mu$ g) of capsaicin and to reduce simultaneously the area of attendant mechanical hyperalgesia in humans.<sup>5</sup> However, the relation between plasma opioid concentration and reduction in pain or hyperalgesia/allodynia in humans has not been examined. One purpose of the current study was to determine the relation between

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plasma opioid concentrations and acute and chronic pain responses to intradermal injection of capsaicin.

Ketamine only reduces pain from intradermal injection of capsaicin after doses that produce unwanted side effects. Recently, amitriptyline and related compounds have been shown to bind to NMDA receptors *in vitro* in low micromolar concentrations<sup>6</sup> and to function as an NMDA antagonist *in vivo*.<sup>7</sup> Intrathecal injection of amitriptyline reduces hyperalgesia after carrageenan inflammation in rats,<sup>8</sup> and amitriptyline is frequently administered systemically to manage neuropathic pain. As part of a series of studies examining potential efficacy of systemic and intrathecal amitriptyline for hyperalgesic pain, we tried to determine amitriptyline's efficacy after acute intramuscular injection alone. Because amitriptyline could enhance the opioid's effects by monoamine reuptake inhibition,<sup>9</sup> we also examined the effect of amitriptyline plus alfentanil in this model.

## Materials and Methods

The study was divided into two parts: an initial study of six volunteers to test the reproducibility of repeated intradermal capsaicin injections over a short time, and a second study of 40 other volunteers to test the effects of study drugs. Both studies were approved by the Clinical Research Practices Committee, written informed consent was obtained, and volunteers reported to the outpatient General Clinical Research Center at 7:00 AM, having had nothing to eat or drink since midnight. The same schedule of capsaicin injections and sensory testing was used in both studies, and each volunteer received an intradermal capsaicin injection on a day before the study to train them in assessing pain and in determining areas of hyperalgesia and allodynia. Volunteers were trained before this test injection of capsaicin to assess pain numerically in response to controlled noxious heat stimuli using a Peltier device. This training using the Peltier device was repeated on the morning of the study before capsaicin injection.

Capsaicin (Fluka Chemie, Buchs, Switzerland) was dissolved in Tween-80 and passed through a 20- $\mu$ m filter before injection. Injections were made in less than 2 s on the volar aspect of the forearm or lateral aspect of the calf in a volume of 10  $\mu$ l containing 100  $\mu$ g capsaicin, and then the needle was immediately removed. Volunteers rated their pain numerically at 15-s intervals for 3 min after injection, then at 5, 10, 20, 30, 60, 120, 180, and 240 min after injection. Areas of hyperalgesia

were determined by sensation of pain to mechanical testing with a calibrated, 225-mN von Frey filament at 5, 10, 15, 30, 45, and 60 min after each injection, then at hourly intervals. Areas of allodynia were determined at these same times to mechanical testing with a cotton applicator attached to a metal band and calibrated to apply 100 g force. In each case, testing was performed from an area of normal sensation until the affected area was reached. Testing was performed along at least four radial spokes, the skin was marked at these points, and marks were transcribed to a clear plastic sheet, and the area was calculated by trapezoidal approximation.

Four capsaicin injections were performed on the day of each study. Volunteers were randomized to receive the first injection in either the upper or lower extremity. The second injection was performed ipsilateral to the first on the other extremity (for example, the first injection in left arm, second injection in left leg). The site of the third injection was opposite the second, and the fourth injection was opposite the second (in this example, the third injection in right leg, the fourth in right arm). Injections were separated by 60 min. In the first part of the study, six volunteers received this regimen of injections to determine whether there was an effect of injection site or order on pain response.

In the second part of the study, an intravenous catheter was inserted in one antecubital vein to administer drug and in an antecubital vein in the contralateral extremity to sample venous blood. Thirty minutes after the second capsaicin injection, volunteers received an intramuscular injection, and the intravenous infusion was started with rate programmed to achieve the first target plasma concentration. Pain, hyperalgesia, and allodynia from the first two injections were considered control values. Thirty minutes after the intramuscular injection/intravenous infusion, volunteers received the third capsaicin injection. Pain responses from this injection were considered to reflect the effect of the first target plasma concentration and the intramuscular injection. Just before the fourth capsaicin injection, the intravenous infusion was adjusted to achieve the second target plasma concentration. Pain responses from this last injection were considered to reflect the effect of the second target plasma concentration and the intramuscular injection. A different batch of capsaicin was prepared for volunteers in the second part of the study than had been used in the first part.

Volunteers were randomized into four drug treatment groups, and neither the volunteer nor the investigator was aware of the assignment. Volunteers re-



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ceived either 4 mg midazolam given intramuscularly plus intravenous saline (considered as an active placebo), 25 mg amitriptyline given intramuscularly plus intravenous saline, 25 mg amitriptyline given intramuscularly plus intravenous alfentanil, or saline given intramuscularly plus intravenous alfentanil. Alfentanil was given by computer-controlled infusion using the STANPUMP algorithm to achieve target plasma concentrations of 50 ng/ml (first target) and 200 ng/ml (second target).

In addition to assessing their pain, patients rated their nausea and sedation on 10-cm visual analog scales (VAS) at hourly intervals after intramuscular drug injection and initiating the intravenous infusion. Venous blood was drawn 5, 15, 30, 60, 90, 120, 180, and 240 min after drug injection. Samples were stored at  $-70^{\circ}\text{C}$  until analysis. At the time of analysis, the code was broken, and only samples in volunteers receiving amitriptyline or alfentanil were analyzed. Amitriptyline plasma concentration was determined by high-pressure liquid chromatography with ultraviolet detection.<sup>10</sup> Sensitivity of the method is 3 ng/ml in the original sample. Alfentanil plasma concentration was determined by radioimmunoassay with interassay coefficient of variation of 4% and detection limit of 0.05 ng/ml.<sup>11</sup>

Data are presented as means  $\pm$  SD or median  $\pm$  25th and 75th percentiles as appropriate. Pain magnitude was estimated by each participant according to their own numeric scale. These estimates were normalized to each person using a ratio whereby 10 reflected the largest pain estimate of that person. This method has been shown to produce linear stimulus response relations to graded pain stimuli in volunteers.<sup>12</sup> In the first part of the study (validation of reproducibility of four injections), pain, hyperalgesia, and allodynia were compared according to site of injection (arm *vs.* leg) and injection order by two-way analysis of variance for repeated measures. In the second part of the study, the effect of drug within each treatment group for pain, hyperalgesia, and allodynia was determined by two-way analysis of variance for repeated measures on ranks, with factors of volunteer and injection order. Groups were compared for amitriptyline and alfentanil plasma concentrations and for VAS sedation and nausea by two-way analysis of variance for repeated measures. Correlation analysis was performed by linear regression. Probability values less than 0.05 were considered significant.

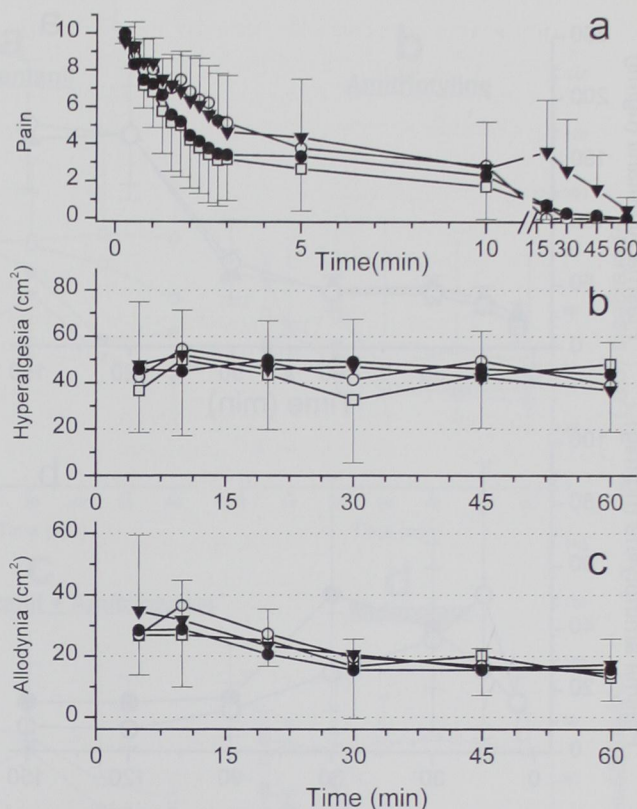


Fig. 1. Magnitude of pain (A), area of hyperalgesia (B), and allodynia (C) after the first (square), second (open circle), third (filled circle), and fourth (closed inverted triangle) hourly intradermal injection of 100  $\mu\text{g}$  capsaicin. For pain, each symbol represents the mean of six volunteers, with  $\pm$  standard deviation and  $\pm$  standard deviation shown for the first and fourth injections, respectively. For hyperalgesia and allodynia, each symbol represents the median of six volunteers, with 75th and 25th percentiles shown for the first and fourth injections, respectively. Injection site was randomly assigned as the right and left upper and lower extremities. No difference was observed in pain response or areas of hyperalgesia or allodynia as a function of injection order.

## Results

### Part 1: Validation Study

The average age of volunteers was 31 yr (range, 19–41 yr), and three were women and three were men. Pain to intradermal capsaicin injection was intense but brief, lasting 5–10 min, and did not differ with injection order (fig. 1A) by analysis of variance. Similarly, there was no effect on pain report of injection site (mean pain score during the first 3 min was  $6.4 \pm 1.8$  after injection in the leg *vs.*  $6.4 \pm 1.8$  in the arm) or sex (mean pain score over the first 3 min was  $5.9 \pm 2.2$  in women and  $6.9 \pm 1.2$  in men). Similarly, areas of



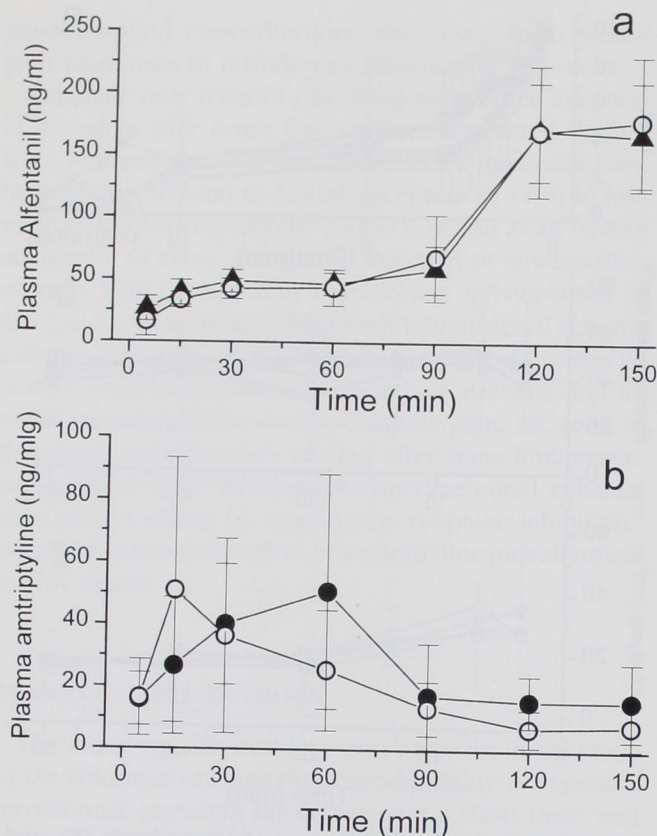


Fig. 2. Plasma alfentanil (A) or amitriptyline (B) concentrations in volunteers randomized to receive alfentanil alone (filled triangle) or with intramuscular amitriptyline (open circle), or amitriptyline alone (filled circle) or with alfentanil (open inverted triangle). Each symbol represents the mean  $\pm$  SD of eight to ten volunteers. No differences were observed between groups, except earlier peak amitriptyline concentrations in the amitriptyline-alfentanil group (see text for details).

hyperalgesia (fig. 1B) and allodynia (fig. 1C) were unaffected by injection order. As with pain, mean area of hyperalgesia over 60 min was similar after injection in the leg ( $46 \pm 20$  cm<sup>2</sup>) as in the arm ( $43 \pm 14$  cm<sup>2</sup>) and was similar in women ( $49 \pm 15$  cm<sup>2</sup>) and in men ( $40 \pm 18$  cm<sup>2</sup>). In addition, mean area of allodynia after 60 min was similar after injection in the arm ( $21 \pm 11$  cm<sup>2</sup>) as in the leg ( $22 \pm 10$  cm<sup>2</sup>), and was similar in women ( $22 \pm 8$  cm<sup>2</sup>) and in men ( $21 \pm 13$  cm<sup>2</sup>). Overall average area of hyperalgesia ( $47 \pm 9.2$  cm<sup>2</sup>) was larger than allodynia ( $24 \pm 4.9$  cm<sup>2</sup>) during first hour ( $P < 0.05$ ) after intradermal capsaicin injection.

### Part 2: Drug Study

Volunteers were aged  $31 \pm 8$  yr, measured  $173 \pm 11$  cm in height, and weighed  $79 \pm 17$  kg. Twenty were

women, and 20 were men. The computer-controlled infusion rapidly achieved and maintained reasonably stable alfentanil concentrations, and amitriptyline did not affect alfentanil concentrations (fig. 2A). The average plasma alfentanil concentrations during the 60 min after the third capsaicin injection were  $52 \pm 10$  ng/ml in those receiving alfentanil alone and  $51 \pm 13$  ng/ml in those receiving alfentanil and amitriptyline. Corresponding values during the 60 min after the fourth capsaicin injection were  $173 \pm 47$  ng/ml and  $182 \pm 47$  ng/ml. Amitriptyline was rapidly absorbed after intramuscular injection (fig. 2B) and peaked in concentration in plasma earlier when given with intravenous injection of alfentanil than when given alone (median of 30 vs. 60 min;  $P < 0.05$ ). Plasma amitriptyline concentrations averaged  $36 \pm 29$  ng/ml and  $26 \pm 23$  ng/ml during the 60 min after the third capsaicin injection in the amitriptyline-alone and amitriptyline-plus-alfentanil treatment groups, respectively. These values do not differ, nor do the average amitriptyline concentrations during the 60 min after the fourth capsaicin injection in these two groups ( $16 \pm 10$  ng/ml and  $8 \pm 7$  ng/ml, respectively).

Pain report after either the third or fourth capsaicin

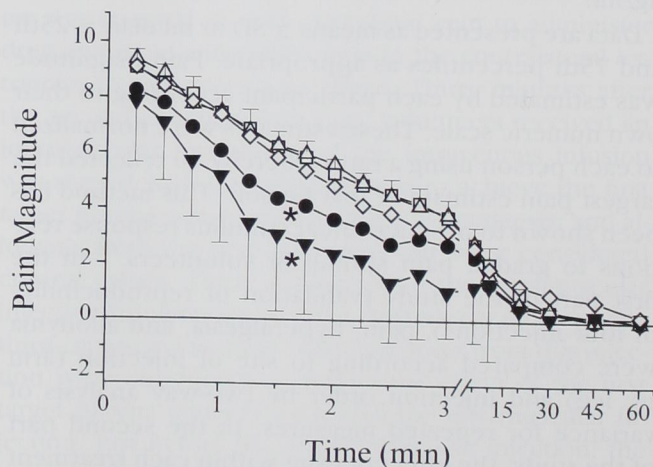
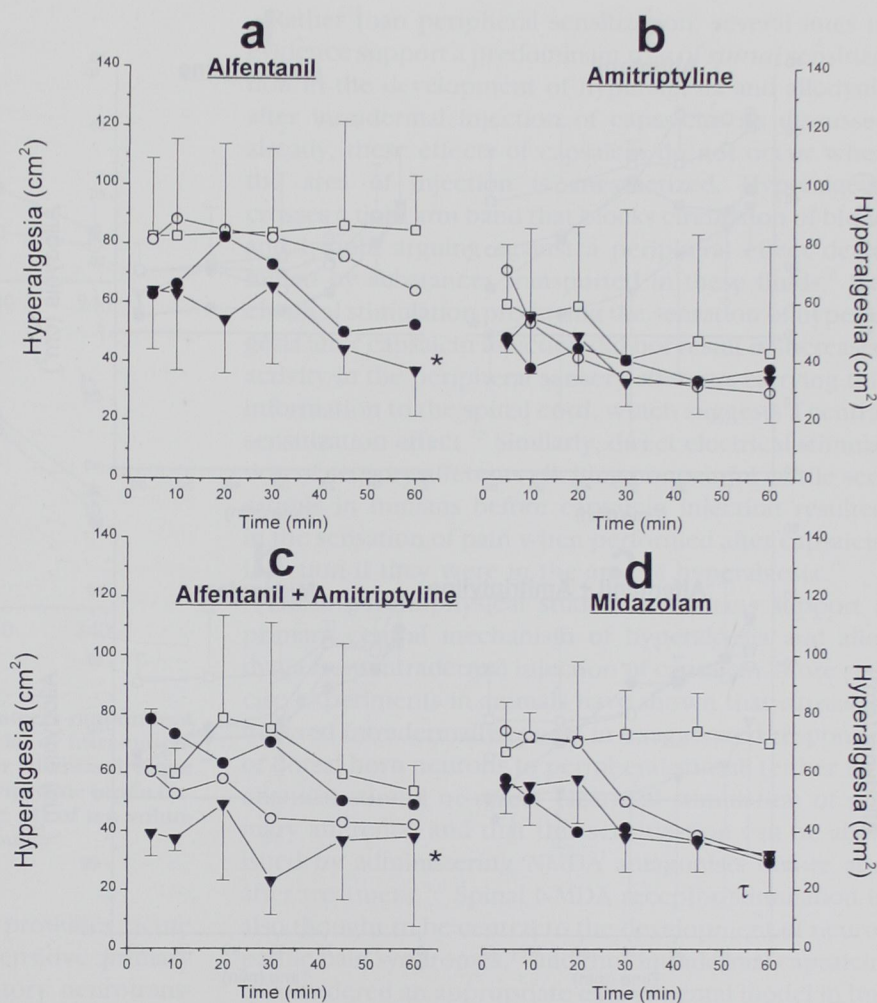


Fig. 3. Magnitude of pain after intradermal injection of capsaicin, averaged for the first two injections (control: open square), or after the fourth capsaicin injection after intramuscular midazolam (open diamond), intramuscular amitriptyline ( $\Delta$ ), intravenous alfentanil (200 ng/ml targeted plasma concentration: filled circle), or the combination of amitriptyline and alfentanil (filled inverted triangle). Each symbol represents the mean of ten volunteers, with  $\pm$  standard deviation and  $\pm$  standard deviation shown for the control and amitriptyline-plus-alfentanil groups, respectively. \* $P < 0.05$  for comparison of alfentanil alone and with amitriptyline to control by two-way analysis of variance.



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Fig. 4. Area of hyperalgesia after the first (open square), second (open circle), third (filled circle), or fourth (filled inverted triangle) intradermal capsaicin injection in volunteers receiving intravenous alfentanil (A), intramuscular amitriptyline (B), alfentanil plus amitriptyline (C), or intramuscular midazolam (D). Each symbol represents the median of ten volunteers, with 75th and 25th percentiles shown for the first and fourth injections, respectively. \* $P < 0.05$  for comparison of the fourth injection of alfentanil alone and with amitriptyline to the first injection.  $\tau P < 0.05$  for second, third, and fourth injections compared with the first.



injection was unaffected by intramuscular injection of midazolam or amitriptyline. Figure 3 shows the response to the first two capsaicin injections, which did not differ among groups, and the averaged response to the third and fourth injections in the midazolam and amitriptyline groups. Similarly, alfentanil, either alone or with amitriptyline, had no effect on acute pain report to the third capsaicin injection (plasma concentration, 51 or 52 ng/ml, as described before). In contrast, alfentanil alone and with amitriptyline decreased pain report after the fourth capsaicin injection (fig. 3; plasma concentration, 173 to 182 ng/ml, as described before). There was a similar, significant correlation between plasma alfentanil concentration and pain report for alfentanil alone ( $r = -0.59$ ,  $P = 0.006$ ) and for alfentanil plus amitriptyline ( $r = -0.57$ ,  $P = 0.01$ ).

Hyperalgesia did not differ in the first 60 min after

the first and second capsaicin injections in volunteers receiving alfentanil or amitriptyline or their combination (figs. 4A–C). In contrast, the area of hyperalgesia was less after the second capsaicin injection than after the first in those receiving midazolam (fig. 4D). Hyperalgesia after the third and fourth capsaicin injections were unaffected by amitriptyline (fig. 4B), whereas hyperalgesia after the fourth injection was similarly reduced in volunteers receiving alfentanil alone (fig. 4A) or with amitriptyline (fig. 4C). Hyperalgesia after the third and fourth capsaicin injections in volunteers receiving midazolam was similar to that after the second injection. There was a significant correlation between plasma alfentanil concentration and reduction in area of hyperalgesia in the alfentanil-plus-amitriptyline group ( $r = -0.52$ ,  $P = 0.02$ ) but not in the alfentanil-alone group.

The response of allodynia to treatments was essen-



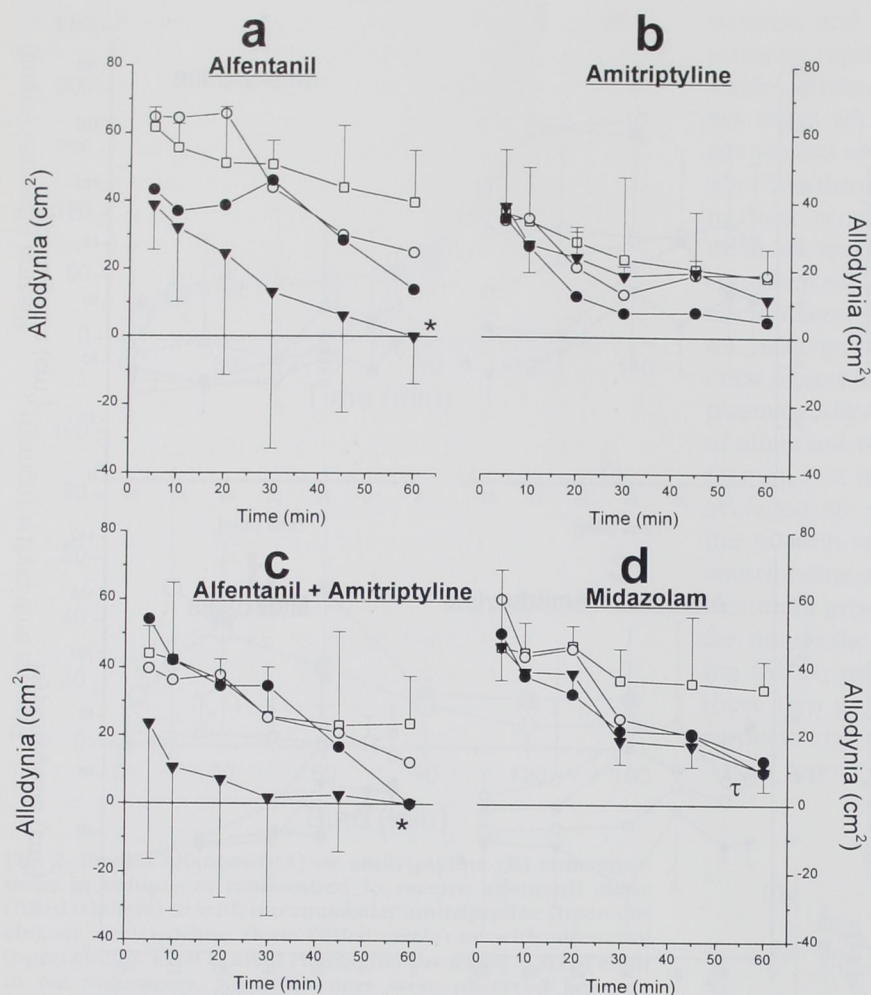


Fig. 5. Area of allodynia after the first (open square), second (open circle), third (filled circle), or fourth (filled inverted diamond) intradermal capsaicin injection in volunteers receiving intravenous alfentanil (A), intramuscular amitriptyline (B), alfentanil plus amitriptyline (C), or intramuscular midazolam (D). Each symbol represents the median of ten volunteers, with 75th and 25th percentiles shown for the first and fourth injections, respectively. \* $P < 0.05$  for comparison of the fourth injection of alfentanil alone and with amitriptyline with the first injection.  $\tau P < 0.05$  for the second, third, and fourth injections compared with the first.

tially the same as that of hyperalgesia and is depicted in the same manner (fig. 5A–D). Similar to hyperalgesia, there was a significant correlation between plasma alfentanil concentration and reduction in area of allodynia in the alfentanil-plus-amitriptyline group ( $r = -0.52$ ,  $P = 0.02$ ) but not in the alfentanil-alone group.

All drugs produced sedation. Sedation was similar in the active control (midazolam) and amitriptyline groups (fig. 6A) and in the alfentanil-alone and alfentanil-plus-amitriptyline groups (fig. 6B). No volunteer experienced nausea after receiving midazolam. One volunteer receiving amitriptyline had nausea rated as 4 on a VAS before drug injection, and this nausea resolved in the ensuing 2 h after drug administration. No other volunteer receiving amitriptyline experienced nausea. Nine of ten volunteers receiving alfentanil alone experienced nausea, which peaked at the end of the infusion (VAS

for nausea,  $2.5 \pm 4.1$  cm). In contrast, only three of ten volunteers receiving alfentanil plus amitriptyline experienced nausea ( $P < 0.05$  vs. alfentanil alone), and nausea in the amitriptyline-alfentanil group was milder by VAS (at the time of peak, at the end of infusion, VAS for nausea was  $0.1 \pm 0.3$  cm).

## Discussion

Intradermal capsaicin injection has been described in a series of studies in volunteers as a method to examine central sensitization and to screen drugs for efficacy against hyperalgesic pain states. The current study provides novel information that validates this model and describes the effects of systemically administered drugs on the model.



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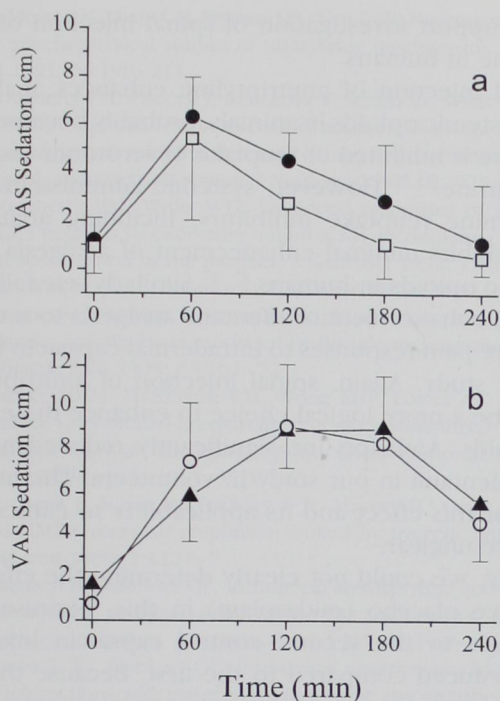


Fig. 6. Visual analog scale sedation in volunteers randomized to receive or amitriptyline alone (filled circle) or intramuscular midazolam alone (open square; A), or alfentanil alone (filled triangle) or with intramuscular amitriptyline (open circle; B). Each symbol represents the mean  $\pm$  SD of ten volunteers. There was no difference between groups.

Intradermal injection of capsaicin produces acute pain by direct stimulation of chemosensitive primary afferents and central release of excitatory neurotransmitters in the spinal cord. In addition, mechanical hyperalgesia and allodynia after intradermal capsaicin results from both peripheral and central sensitization. These pain responses depend on the initial stimulus from the capsaicin injection, because they do not occur when the capsaicin is injected in skin that has been anesthetized by infiltration with local anesthetic or by peripheral nerve block.<sup>2</sup> Support for peripheral sensitization comes primarily from observations: increased ongoing activity in a minority of peripheral single units in humans in the area of hyperalgesia,<sup>13</sup> reduction in the area of hyperalgesia by cooling the skin in the receptive area,<sup>13</sup> and block of spread of the area of hyperalgesia beyond a line of local anesthetic infiltration.<sup>2</sup> However, peripheral sensitization alone does not explain the development of hyperalgesia and allodynia, because local cooling reduces but does not abolish these effects, and most primary afferent units fail to exhibit ongoing discharge or enhanced responses to stimuli.

Rather than peripheral sensitization, several lines of evidence support a predominant role of *spinal* sensitization in the development of hyperalgesia and allodynia after intradermal injection of capsaicin. As discussed already, these effects of capsaicin do not occur when the area of injection is anesthetized. Hyperalgesia crosses a tight arm band that blocks circulation of blood and lymph, arguing against a peripheral effect determined by substances transported in these fluids.<sup>2</sup> Mechanical stimulation producing the sensation of hyperalgesia after capsaicin injection did not result in increased activity in the peripheral sensory afferents carrying this information to the spinal cord, which suggests a central sensitization effect.<sup>13</sup> Similarly, direct electrical stimulation of sensory afferents eliciting nonpainful tactile sensations in humans before capsaicin injection resulted in the sensation of pain when performed after capsaicin injection if they were in the area of hyperalgesia.<sup>14</sup>

These psychophysical studies in humans support a primary central mechanism of hyperalgesia and allodynia from intradermal injection of capsaicin. More precise experiments in animals have shown that capsaicin injected intradermally results in exaggerated responses of dorsal horn neurons to peripheral stimuli (either mechanical stimuli or direct electrical stimulation of primary afferents) and that this sensitization can be abolished by administering NMDA antagonists before and after treatment.<sup>3,4</sup> Spinal NMDA receptor stimulation is also thought to be central to the development of neuropathic pain syndromes,<sup>15</sup> and thus intradermal capsaicin is considered an appropriate experimental model in humans to examine the pharmacology of pain produced experimentally.

Previous investigators have shown the dose-dependent pain responses from intradermal capsaicin in humans,<sup>1</sup> but this is the first validation of four repeated injections in one experimental setting and comparison of effects when the drug is injected in the upper *versus* lower extremity. We chose this rotating series of injections in all four extremities in one session to subsequently test the dermatomally restricted action of spinally administered drugs. The current results suggest no effect of injection site or order in capsaicin-induced responses, supporting this model for subsequent studies.

Previous reports show that intravenous alfentanil reduces ongoing pain, hyperalgesia, and allodynia in volunteers receiving intradermal capsaicin<sup>5</sup> and in patients with chronic pain after trauma.<sup>16</sup> However, the previous two studies dosed alfentanil to the onset of side effects



in a non-steady-state manner and did not determine the relation between plasma concentration and analgesic effect. In contrast, our study used computer-controlled infusion to rapidly achieve and maintain plasma concentrations of alfentanil in the analgesic range to acute experimental<sup>17</sup> or postoperative pain.<sup>18</sup> The results fail to show a selective reduction in hyperalgesia and allodynia by systemic alfentanil, because only high plasma concentrations, which also reduced acute pain to injection, reduced these elicited responses. Opioids can reduce spinal glutamate release after capsaicin injection in animals,<sup>19</sup> but the results of the current study correspond with the previous human studies in demonstrating that this only occurs in humans receiving large systemic doses accompanied by bothersome side effects. Although we could not determine the mechanism of opioid effect, the simultaneous reduction in acute pain from injection and development of hyperalgesia and allodynia suggest an action in reducing the spinal cord effects of the afferent barrage from the intradermal capsaicin rather than a specific effect on hyperalgesia and allodynia *per se*.

Amitriptyline produces analgesia in patients with neuropathic pain,<sup>20</sup> although its mechanism of action is not understood. Recent studies demonstrating an NMDA antagonist property of amitriptyline<sup>21</sup> suggest that amitriptyline may reduce neuropathic pain by this mechanism, and studies in animals show reversal of inflammatory and NMDA-induced hyperalgesia by spinal amitriptyline.<sup>8</sup> Other studies have found reductions in ongoing pain, hyperalgesia, and allodynia by systemic administration of NMDA antagonists (ketamine or dextromethorphan) in patients with neuropathic pain<sup>16,22</sup> and in volunteers receiving intradermal injections of capsaicin,<sup>5</sup> but only at doses that produced symptoms of intoxication. We could not observe any such effect of amitriptyline alone in our study, although the dose administered was sufficient to produce sedation. It is possible, therefore, that amitriptyline fails to act as an NMDA antagonist in this model and in patients with chronic pain, who typically achieve pain relief only after weeks of amitriptyline administration. On the other hand, it could also reflect inability to achieve sufficient concentrations of amitriptyline in the spinal cord after acute systemic administration to affect these elicited responses. Other researchers have suggested that future treatment of neuropathic pain with fewer side effects may be possible with spinal administration of NMDA antagonists,<sup>16,22</sup> and we are performing toxicology stud-

ies to support investigation of spinal injection of amitriptyline in humans.

Spinal injection of amitriptyline enhances analgesia from systemic opioids in animals, probably because amitriptyline is inhibited of reuptake of serotonin and norepinephrine.<sup>23,24</sup> However, systemic administration of monoamine reuptake inhibitors, including amitriptyline, exhibits minimal enhancement of analgesia from systemic opioids in humans.<sup>25-27</sup> Similarly, we failed to observe enhancement of alfentanil analgesia to acute or subacute pain responses to intradermal capsaicin in the current study. Again, spinal injection of amitriptyline would be a more logical choice to enhance the effects of opioids. Amitriptyline significantly reduced nausea from alfentanil in our study in volunteers. The mechanism for this effect and its applicability to clinical settings are unclear.

Finally, we could not clearly determine the effect of an active placebo (midazolam) in this, because pain responses to the second control capsaicin injection were reduced compared to the first. Because the last two injections were similar to the second, we could either conclude that midazolam had an analgesic effect (compared with first injection) or that it did not (compared with the second injection). Although not conclusive, a previous study of human volunteers showed no effect of midazolam (mean dose, 3.4 mg) on ongoing pain, hyperalgesia, and allodynia after intradermal injection of capsaicin.<sup>5</sup>

In summary, acute pain, hyperalgesia, and allodynia are similar in four repeated intradermal injections of capsaicin during 4 h in the leg and arm of volunteers. Systemically administered alfentanil reduces all these pain responses, but only at high plasma concentrations (more than 150 ng/ml) associated with side effects. Amitriptyline in a dose causing acute sedation did not affect these pain responses, nor did it enhance alfentanil's effects. Ongoing studies are aimed at introducing spinal injection of amitriptyline into clinical trials as a more effective route of administration in the treatment of neuropathic pain.

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