Differential Modulation of Remifentanil-induced Analgesia and Postinfusion Hyperalgesia by S-Ketamine and Clonidine in Humans

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Background: Experimental studies and clinical observations suggest a possible role for opioids to induce pain and hyperalgesia on withdrawal. The authors used a new experimental pain model in human skin to determine the time course of analgesic and hyperalgesic effects of the µ-receptor agonist remifentanil alone or in combination with the N-methyl-D-aspartate-receptor antagonist S-ketamine or the α2-receptor agonist clonidine.

Methods: Thirteen volunteers were enrolled in this randomized, double-blind, placebo-controlled study. Transcutaneous electrical stimulation at a high current density (2 Hz, 67.3 ± 16.8 mA, mean ± SD) induced acute pain (numerical 11-point rating scale: 5–6 out of 10) and stable areas of mechanical hyperalgesia to punctate stimuli and touch (allodynia). The magnitude of pain and area of hyperalgesia were assessed before, during, and after drug infusion (remifentanil at 0.1 µg/kg-1 · min-1 and S-ketamine at 5 µg/kg-1 · min-1 over a period of 30 min, respectively; clonidine infusion at 2 µg/kg for 5 min).

Results: Remifentanil reduced pain and areas of punctate hyperalgesia during infusion. In contrast, postinfusion pain and hyperalgesia were significantly higher than control. During infusion of S-ketamine, pain and hyperalgesia decreased and gradually normalized after infusion. When given in combination, S-ketamine abolished postinfusion increase of punctate hyperalgesia but did not reduce increased pain ratings. Clonidine alone did not significantly attenuate pain or areas of hyperalgesia. However, when given in combination with remifentanil, clonidine attenuated postinfusion increase of pain ratings.

Conclusions: Opioid-induced postinfusion hyperalgesia could be abolished by S-ketamine, suggesting an N-methyl-D-aspartate-receptor mechanism. In contrast, elevated pain ratings after infusion were not reduced by ketamine but were alleviated by the α2-receptor agonist clonidine. The results of this study suggest different mechanisms of opioid-induced postinfusion antianalgesia and secondary hyperalgesia.

OPIOIDS have been hypothesized to prevent postoperative pain when administered during surgery. However, instead of improved postoperative analgesia, recent clinical studies suggest that on their withdrawal, opioids can even enhance pain sensitivity.1,2 Activation of N-methyl-D-aspartate (NMDA)-receptors by µ-receptor agonists has been assumed to be an underlying mechanism,3,4 but experimental evidence from humans could not yet be provided because a suitable model was lacking. Recently, a new human model of electrically evoked pain and secondary hyperalgesia was introduced that is suitable to test the analgesic and antihyperalgesic effects of anesthetics.5

The present work was designed to determine mechanisms of opioid-induced antianalgesia and hyperalgesia in humans. Therefore, we first studied the effects of the short-acting µ-receptor agonist remifentanil, the NMDA-receptor antagonist S-ketamine, or clonidine during and after infusion in the model of electrically evoked pain and secondary hyperalgesia described above. Because it has been suggested that opioids might interfere with NMDA- and α2-receptors, the effects of the remifentanil infusion were compared with a combination of the µ-receptor agonist with either S-ketamine or clonidine.

Materials and Methods

Thirteen healthy men were enrolled in this randomized, crossover, double-blind, and placebo-controlled study. The average age was 31.2 ± 5.3 yr (range, 20–40 yr). All subjects were familiarized with study procedures before participation. No subject had a known drug allergy or was taking medication that might interfere with itch or pain sensations and flare response (i.e., analgesics, antihistamines, or calcium or sodium channel blockers). Each subject gave informed consent to take part in the study; the experiments were performed in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of the Medical Faculty of the University of Erlangen-Nuremberg.

Experimental Pain Models

Transdermal electrical stimulation was used to induce ongoing pain and secondary mechanical hyperalgesia as described previously.5 Briefly, a stainless steel needle (Nicolet-EME, Kleinostheim, Germany) was inserted intradermally to a length of 1 cm at the central volar forearm of the subjects. A skin surface electrode (1.0 cm in diameter) was placed at the center of the needle for stimulation. The current was gradually in-
Drug infusion

Remifentanil
S-Ketamine
Clonidine

0.1 μg/kg/min
5 μg/kg/min
2 μg/kg

Ongoing Pain
Pinprick-hyperalgesia
Allodynia

Electric stimulation

Fig. 1. Schematic illustration of the experimental protocol. The subjects received hidden intravenous infusions of remifentanil (0.1 μg · kg⁻¹ · min⁻¹ for 30 min), S-ketamine (5 μg · kg⁻¹ · min⁻¹ for 30 min), or clonidine (2 μg/kg over a period of 5 min). Ongoing pain and areas of punctate hyperalgesia and allodynia were determined repeatedly.

creased during the first 15 min of stimulation, targeting a pain rating of 5 to 6 (out of 10) and then was kept constant for the remaining time of the experiment.

Medication and Side Effects

In six separate treatment trials at least 1 week apart, subjects received hidden intravenous infusions of remifentanil at 0.1 μg · kg⁻¹ · min⁻¹ for 30 min, S-ketamine at 5 μg · kg⁻¹ · min⁻¹ for 30 min, clonidine at 2 μg/kg over a period of 5 min, or saline. In addition, combinations of remifentanil with either ketamine or clonidine at the above-described infusion rates were applied (fig. 1). All subjects received the single infusions first; they were randomized by Latin square. For the combined infusions, the sequence was alternated between the subjects. Neither the subjects nor the experimenter who was responsible for the psychophysics handled the infusions, and both had no direct view of them.

During the infusion, an examiner asked the subjects about their side effects as sedation, dizziness, pruritus, or nausea. Oxygen saturation measured by pulse oximetry (Spo₂), ECG, and noninvasive arterial pressure were monitored continuously during the time of the study.

Sensory Testing

During an experiment, a second examiner asked the subject to rate the intensity of ongoing pain induced by the electrical stimulation every 5 min on a numerical 11-point rating scale). The end points of the scale were defined as “no pain” (0) and “maximum pain” (10). The area of punctate hyperalgesia was determined with a 450-mN von Frey filament (Stoelting, Chicago, IL), and the area of touch-evoked allodynia was determined with a cotton-wool tip gently stroked on the skin. The borders of the hyperalgesic areas were determined by moving along four linear paths parallel and vertical to the axis of the forearm from distant starting points toward the stimulation site until the volunteer reported increased pain sensations evoked by the von Frey filament (punctate hyperalgesia) or unpleasant sensations evoked by stroking the skin with the cotton wool (allodynia). These sites were marked on the skin and traced on an acetate sheet at the end of the experiment. For further analysis, both diameters were used to estimate the areas of secondary hyperalgesia (D/2 x d/2 x π).

Statistical Analysis

All results were expressed as mean ± SD. Treatment effects over time were evaluated by two-way repeated-measures ANOVA; Scheffé tests were performed as post hoc tests. Because of possible biphasic effects over time (analgesia vs. hyperalgesia), comparisons between treatments were analyzed separately during and after infusion. Differences between treatments at individual time points were compared by use of planned comparisons, corrected with the Bonferroni procedure. Significance levels throughout this study were P = 0.05.

Results

Transdermal Stimulation

To achieve a pain rating of 5–6, the average current was increased to 67.3 ± 16.8 mA (range, 30–90 mA) during the first 15 min of intradermal electrical stimulation. Thereafter, pain ratings decreased significantly from 5.5 ± 0.5 to 3.6 ± 1.1 (F₁₂,₂₅₈ = 20.73, P < 0.001; Scheffé test, P < 0.001 at 80 min and remaining time), whereas areas of punctate hyperalgesia increased from 37.1 ± 14.1 to 46.2 ± 20.9 cm² (F₈,₉₆ = 2.31, P < 0.05; Scheffé test, P = not significant [NS]). The allodynic areas remained stable during the intradermal electrical stimulation (F₈,₉₆ = 0.13, P = NS).

Remifentanil Infusion

Infusion of remifentanil 0.1 μg · kg⁻¹ · min⁻¹ led to a fast onset of analgesia. After 30 min of infusion, calculated plasma levels reached a steady state (fig. 2, A). During this time, almost all subjects developed subjective side effects, primarily a moderate sedation, which generally appeared after 10 min of infusion time and was paralleled by a slight decrease in oxygen saturation (F₁₂,₁₄₄ = 4.87, P < 0.001) (fig. 2, B). However, all subjects felt comfortable and answered promptly to the questions of the investigators, and assessments of hyperalgesic areas were accurate and reproducible. At no time did subjects complain of bothersome side effects; heart rate and blood pressure remained unchanged.

Remifentanil significantly decreased pain ratings during the infusion compared with control (F₅,₆₀ = 24.40, P < 0.001) (fig. 2, C). However, shortly after cessation of the infusion, pain ratings increased and exceeded control values (F₁₁,₁₅₂ = 28.71, P < 0.001). This antianalgesic effect was most prominent at 30 min after cessation of infusion. Therefore, ratings gradually declined but
In addition, areas of punctate hyperalgesia were significantly reduced during infusion of S-ketamine (F2,24 = 5.76, P < 0.001) (fig. 3, D). However, this antihyperalgesic effect was only short-lasting; 15 min after cessation of the infusion, hyperalgesic areas increased and reached control values (F3,36 = 3.36, P < 0.05) (fig. 3, D).

Alldynic areas were not affected by S-ketamine. Although alldynic areas were slightly decreased, this failed to be significant (F2,24 = 0.82, P = NS and F3,36 = 1.63, P = NS, during and after infusion, respectively) (fig. 3, E).

Clonidine Infusion

Because of its long terminal half-time, clonidine plasma levels after a 5-min intravenous infusion of 2 μg/ml have to be assumed to be still elevated at the end of the observation period (fig. 4, A). During this time, oxygen saturation (F12,144 = 4.91, P < 0.001) and blood pressure (F12,144 = 12.56, P < 0.001) were significantly decreased compared with control (fig. 4, B). Almost all subjects developed moderate sedation after clonidine infusion. However, all subjects felt comfortable and answered promptly to the questions of the investigators.

No effect of clonidine on pain ratings and areas of secondary hyperalgesia was observed in our model of intradermal electrical stimulation (fig. 4, C, D, and E, respectively).
Coadministration of Remifentanil and \textit{S}-Ketamine

Coadministration of remifentanil and \textit{S}-ketamine resulted in a significant decrease in oxygen saturation compared with remifentanil alone (F_{12,144} = 2.20, P < 0.05 by ANOVA; oxygen saturation measured by pulse oximetry (SpO2) and heart rate (HR) remained unchanged (P = NS by ANOVA) (B). Pain ratings (C) and areas of punctate hyperalgesia (D) were reduced significantly during infusion of \textit{S}(-)-ketamine (P < 0.05 by ANOVA for each). Areas of touch-evoked alldynia (E) were not affected by \textit{S}-ketamine (P = NS by ANOVA). Data are expressed as mean ± SD (n = 13), *P < 0.05, planned comparisons corrected with the Bonferroni procedure. NRS = numerical rating scale.

Fig. 3. Time course of calculated \textit{S}-ketamine plasma concentrations after a constant-rate infusion of 5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) (shaded areas). The calculation was based on a data sheet from the literature\(^5\) exemplary for a 75-kg subject (A). Infusion of \textit{S}(-)-ketamine resulted in a significant increase in the mean arterial pressure (MAP) (P < 0.05 by ANOVA); oxygen saturation measured by pulse oximetry (SpO2) and heart rate (HR) remained unchanged (P = NS by ANOVA) (B). Pain ratings (C) and areas of punctate hyperalgesia (D) were reduced significantly during infusion of \textit{S}(-)-ketamine (P < 0.05 by ANOVA for each). Areas of touch-evoked alldynia (E) were not affected by \textit{S}-ketamine (P = NS by ANOVA). Data are expressed as mean ± SD (n = 13), *P < 0.05, planned comparisons corrected with the Bonferroni procedure. NRS = numerical rating scale.

A

B

C

D

E

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In addition, coadministration of \textit{S}-ketamine decreased allodynic areas during infusion ($F_{4,48} = 2.69$, $P < 0.05$ by ANOVA) (fig. 5, D) and after infusion ($F_{6,72} = 3.04$, $P < 0.05$; Scheffé tests, $P = 0.05$ compared with control and with remifentanil alone).

Coadministration of Remifentanil and Clonidine

Coadministration of remifentanil and clonidine led to significantly decreased oxygen saturations, especially during the time of remifentanil infusion (minimum, 88 ± 11%) ($F_{2,144} = 3.76$, $P < 0.001$) (fig. 6, A). As observed for clonidine alone, blood pressure was significantly decreased ($F_{12,144} = 8.23$, $P < 0.001$), whereas heart rate remained unchanged (fig. 6, A). Moderate sedation was observed in all subjects; however, they all felt comfortable and answered promptly and reproducibly to the questions of the investigators.

Although clonidine alone failed to produce analgesic effects, coadministration of clonidine and remifentanil decreased pain ratings ($F_{10,120} = 9.17$, $P < 0.001$; Scheffé test, $P < 0.05$) (fig. 6, B). Furthermore, clonidine significantly diminished enhanced pain ratings after cessation of remifentanil infusion ($F_{22,264} = 12.34$, $P < 0.001$; Scheffé test, $P = NS$ compared with control; $P < 0.05$ compared with remifentanil alone).

Coadministration of clonidine reduced areas of postinfusion hyperalgesia compared with remifentanil alone ($F_{0.72} = 3.18$, $P < 0.01$; Scheffé test, $P < 0.05$) (fig. 6, C), and hyperalgesic areas were no longer significantly different from control (Scheffé test, $P = NS$).

Alldyinic areas were not affected by coadministration of clonidine either during remifentanil infusion ($F_{4.48} = 1.34$, $P = NS$) or after the infusion ($F_{6,72} = 1.76$, $P = NS$) (fig. 6, D).

Fig. 5. Coadministration of \textit{S}-ketamine resulted in a significant decrease in oxygen saturation measured by pulse oximetry (SpO$_2$) compared with remifentanil alone ($P < 0.05$ by ANOVA) (A). Remifentanil-induced pain ratings (B) and areas of punctate hyperalgesia (C) and touch-evoked allodynia (D) were significantly reduced during coadministration of \textit{S}-ketamine ($P < 0.05$ by ANOVA for each); however, \textit{S}-ketamine did not affect remifentanil-induced postinfusion antianalgesia ($P = NS$ by ANOVA) (B). Data are expressed as mean ± SD ($n = 13$), $P < 0.05$, planned comparisons corrected with the Bonferroni procedure. NRS = numerical rating scale.

Fig. 6. Coadministration of remifentanil and clonidine resulted in a significant decrease in oxygen saturation measured by pulse oximetry (SpO$_2$) and mean arterial pressure (MAP) compared with remifentanil alone ($P < 0.001$ by ANOVA for each) (A). Coadministration of clonidine shortened the onset of remifentanil-induced analgesia and decreased remifentanil-induced postinfusion antianalgesia ($P < 0.001$ by ANOVA) (B) and punctate hyperalgesia ($P < 0.001$ by ANOVA) (C). Areas of touch-evoked allodynia were not affected (D) ($P = NS$ by ANOVA for each). Data are expressed as mean ± SD ($n = 13$), $P < 0.05$, planned comparisons corrected with the Bonferroni procedure. NRS = numerical rating scale.
Discussion

Our results provide clear experimental evidence for the existence of opioid-induced antianalgesia and hyperalgesia after short-term application in humans and their differential modification by NMDA-receptor antagonists and α₂-receptor agonists.

Medication

The doses for the continuous constant-dose infusions of remifentanil were chosen according to previous studies in which an infusion rate of 0.1 μg · kg⁻¹ · min⁻¹ was found to be effective and safe in healthy volunteers and in postoperative pain control. In accordance with these findings, no respiratory depression was observed; however, a slight decrease in oxygen saturation was noted in almost every subject. S-Ketamine was administered in a “low-dose” regimen, which was defined as an infusion rate less than 20 μg · kg⁻¹ · min⁻¹ (of the racemate) and which was shown to improve postoperative pain management and to reduce opioid-related adverse effects.

The same was true for clonidine: an intravenous bolus injection of 2 μg/kg was shown to enhance opioid-mediated analgesia in postoperative pain states with minimal side effects. However, coadministration of remifentanil and clonidine significantly increased the number of episodes with oxygen desaturation. Although all subjects felt comfortable and answered promptly to the questions of the investigators, this fact may limit the use of this combination for postoperative pain control.

Punctate Hyperalgesia

Remifentanil significantly reduced the area of secondary mechanical hyperalgesia during its infusion. This effect is in accordance with recent publications reporting antihyperalgesic effects of opioids with intradermal capsaicin injection, thus showing similarities between the two different pain models. However, the antihyperalgesic effect of remifentanil turned into a hyperalgesic effect in the postinfusion period. Opioid-induced hyperalgesia has been observed in animal models. A trend toward larger areas of mechanical hyperalgesia after alfentanil and remifentanil was reported in a modified capsaicin model in humans as well.

Several mechanisms have been hypothesized to account for opioid-induced pronociceptive effects. They include opioid-induced up-regulation of the cyclic adenosine monophosphate pathway and spinal dynorphin release, which enhances excytosis of excitatory amino acids and down-regulates spinal glutamate transporters. However, because these processes require longer application periods, their role in our experimental protocol is unclear. Activation of the NMDA-receptor system by opioids has been identified to account for opioid-induced hyperalgesia. In fact, combining remifentanil with the NMDA-receptor antagonist ketamine has been shown to reduce postoperative opioid requirement.

In our study, S-ketamine abolished remifentanil-induced postinfusion hyperalgesia, supporting a major role of NMDA-receptors in its generation.

There is evidence for synergistic effects of NMDA antagonists and opioids from animal work. However, in clinical studies, unequivocal results were obtained. The results of our study reflect the ambiguity observed in the clinical studies: S-ketamine clearly reduced postinfusion hyperalgesia, suggesting that the NMDA-receptor is crucially involved in the generation of opioid-induced hyperalgesia. However, it would be of major clinical relevance to evaluate the long-term hyperalgesic effects of remifentanil infusions with or without coadministration of S-ketamine or clonidine, because a delayed hyperalgesia was reported in animal models.

Acute Pain

Remifentanil reduced electrically induced pain during a short-term infusion, but this analgesic effect turned into a pronociceptive analgesic effect in the postinfusion period. This result is in line with reports on opioid-induced pronociceptive effects in rat. Moreover, it confirms clinical observations of increased postoperative pain and morphine requirement after remifentanil. However, a pronociceptive effect was not observed in a recent study using alfentanil in this pain model. Therefore, the increasing pain ratings shortly after termination of the remifentanil infusion might well reflect a withdrawal reaction caused by the rapid offset of action of remifentanil. Furthermore, differences in opioid-receptor interactions have to be considered as well. In line with this hypothesis, systemic remifentanil but not morphine induced µ-opioid-receptor internalization in rat spinal cord. Internalization and concomitant inactivation of µ-opioid receptors, in turn, will render these cells less susceptible to endogenous or exogenous opioids until the receptors recycle. Clinically, these differences would clearly indicate the importance of an adequate pain therapy after discontinuation of remifentanil infusion, especially for surgical procedures in which moderate or severe postoperative pain is expected.

During combined application of S-ketamine and remifentanil, electrically induced pain was significantly reduced compared with remifentanil alone. However, this effect was observed only during the application. In the postinfusion period, pain ratings increased above control levels and reached the same level as seen after remifentanil alone. Thus, S-ketamine abolished opioid-induced postinfusion hyperalgesia but did not alleviate postinfusion antianalgesia. Differential effects of NMDA blockers on opioid-induced tolerance has been reported for analgesia versus hyperthermia or for opioid sensitization versus tolerance, but as yet, the mechanisms by which the differential effects of S-ketamine on hyperalgesia and antianalgesia might be explained are unclear.
The α₂-receptor agonist clonidine given intravenously had no analgesic or antihyperalgesic effects in our study. This result is in accordance with the lack of antihyperalgesic effects of intravenous clonidine in the capsacin model, whereas intrathecal and epidural application reduced pain and hyperalgesia. These results confirm synergistic analgesic effects of α₂-receptor agonists and opioids that have been reported previously. N-type Ca channels and pertussis-sensitive G proteins have been reported to be involved, but the underlying mechanism of the synergistic effect is largely unknown. It is of potential clinical relevance that the synergism between opioids and α₂-receptor agonists has also been found in neuropathic pain and in inflammatory pain models.

In accordance with these findings, the route of administration and plasma concentrations of the α₂-receptor agonists seemed to be of major relevance also for postoperative pain control. Epidural administration of clonidine has been documented to produce adequate analgesia, but only high doses of intravenous clonidine were analgesic when given alone, whereas lower doses of clonidine were effective only when administered together with opioids.

In addition to the synergistic effect during their application, remifentanil-induced postinfusion hyperalgesia and antialgesia were alleviated by clonidine. Clonidine reduced the intensity of postinfusion antialgesia and hyperalgesia, but they did not decrease below control levels. This effect has certain similarities with the reduction of opioid withdrawal reaction by clonidine, in which adrenergic descending inhibitory systems seem to be of potential relevance. Activating the α₂-adrenoceptor triggers an inwardly rectifying potassium conductance in dorsal horn neurons that causes hyperpolarization and reduced excitability, thus partially mimicking opioid-receptor activation.

**Allodynia**

As shown for the punctate hyperalgesia, remifentanil significantly reduced the area of allodynia during its infusion. However, areas hyperalgesic to touch showed a greater variance than areas hyperalgesic to punctate stimuli. Again, this is consistent with previously published literature on intradermal capsaicin. Thus, hyperalldynamic effects after cessation of remifentanil infusion did not reach a statistically significant level. Coadministration of δ-ketamine further decreased alldynamic areas during and after the infusion, which is in line with previous reports in humans.

**Summary**

Our results provide clear experimental evidence for the existence of opioid-induced antialgesia and hyperalgesia in humans. Cessation of a short-lasting infusion of remifentanil caused a significant antialgesic effect, possibly reflecting opioid withdrawal. The results suggest a modulating effect of the α₂-receptor agonist in opioid-induced postinfusion antialgesia and hyperalgesia. Different mechanisms were suggested for opioid-induced antialgesia and secondary hyperalgesia, because only the latter was prevented by the NMDA-receptor antagonist. Although our experimental setting resembles many aspects of the perioperative situation, it does not allow us to deduce specific therapeutic procedures from the results. Instead, they may help to clarify underlying mechanisms of pain and hyperalgesia and thereby further develop therapeutic concepts for clinical application.

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