The Effect of Naloxone on Ketamine-induced Effects on Hyperalgesia and Ketamine-induced Side Effects in Humans

Søren Mikkelsen, M.D.,* Susanne Ilkjær, M.D.,† Jannick Brennum, M.D., Ph.D.,‡ Finn M. Borgbjerg, M.D.,§ Jørgen B. Dahl, M.D., Ph.D.*

Background: The (NMDA) receptor plays a significant role in wind-up and spinal hypersensitivity and is involved in the occurrence of secondary hyperalgesia. Ketamine is an NMDA-receptor antagonist and has proven effective in alleviating secondary hyperalgesia in humans. Although it is disputed, the actions of ketamine have been ascribed not only to NMDA receptor antagonism, but also to opioid receptor agonism. A study therefore was designed in which the abolishment of a previously demonstrated effect of ketamine on secondary hyperalgesia was sought by pretreatment with naloxone.

Methods: Twenty-five volunteers were subjected to three treatment regimens. A standardized first-degree burn injury was induced. On appearance of primary and secondary hyperalgesia, one of the following infusion schemes was applied in a randomized, double-blind, cross-over fashion: (1) infusion of naloxone (0.8 mg/15 min followed by 0.4 mg/h), succeeded by infusion of ketamine (0.3 mg·kg⁻¹·15 min⁻¹ followed by 0.3

mg·kg⁻¹·h⁻¹); (2) infusion of placebo, succeeded by infusion of ketamine (0.3 mg·kg⁻¹·15 min⁻¹ followed by 0.3 mg·kg⁻¹·h⁻¹); and (3) infusion of placebo, succeeded by infusion of placebo. Heat-pain detection thresholds, magnitude of secondary hyperalgesia around the burn injury, and side effects were determined.

Results: Ketamine reduced secondary hyperalgesia. Naloxone did not affect the action of ketamine. The magnitudes of side effects were equal if the subjects received ketamine, regardless of preceding infusion of naloxone.

Conclusions: In this experimental setting, opioid receptor blockade does not inhibit ketamine-induced reductions of secondary hyperalgesia. (Key words: Blockade; NMDA; N-methyl-D-aspartate; opioid.)

Experimental studies indicate that the N-methyl-D-aspartate (NMDA) receptor plays a significant role in wind-up and spinal hypersensitivity.¹,² Ketamine is an NMDA-receptor antagonist,³ and in experimental settings has proven effective in alleviating secondary hyperalgesia in humans.⁴,⁵ Furthermore, ketamine has been applied successfully in the management of otherwise difficult pain states,⁶-⁸ and ketamine may even eliminate wind-up-like pain.⁹ It is clear that the actions of ketamine are brought about by noncompetitive antagonism at the phencyclidine site in the NMDA receptor complex. It has been suggested, however, that parts of the effect of ketamine could be ascribed to an opioid receptor agonism. Interaction of ketamine with opioid receptors in rats has been reported.¹⁰ Also in rats, the analgesic effect of ketamine has been antagonized by injecting naloxone, thus suggesting that at least part of the action of ketamine is achieved by interaction with opioid receptors.¹¹ Ketamine has been suggested to act partly as a κ-opioid agonist, and the psychotomimetic effects of ketamine in part may be ascribed to κ-receptor binding.¹² Other researchers have found that efficient analgesic effect of ketamine may in part be mediated by the opioid μ-receptor.¹³ Supporting the notion that ketamine at least partly acts by interacting with opioid
receptors, Stella et al.\textsuperscript{14} were able to counteract ketamine-induced anesthesia by injecting naloxone, 0.006 mg/kg in humans.

Thus, there seems to be evidence for an opioid-mediated effect of ketamine, apart from the well-known NMDA-receptor antagonism. On the other hand, contradictory results have been obtained, as Hao et al.\textsuperscript{15} were unable to demonstrate any opioid receptor-mediated effect of ketamine in spinal preparations, and other researchers have also failed to show any effects of ketamine on opioid receptors.\textsuperscript{16}

To investigate a possible opioid receptor-mediated effect of ketamine, an experimental model that has previously shown ketamine to inhibit secondary hyperalgesia in humans was used.\textsuperscript{4} Also, this model has been shown to be sensitive to opioid-mediated analgesia, and naloxone has been shown to inhibit this analgesic effect.\textsuperscript{17}

This experimental model uses the fact that cutaneous heat injury in humans evokes allodynia and hyperalgesia for mechanical and thermal stimuli within an injured area (primary hyperalgesia) and allodynia for mechanical, but not thermal, stimuli in an area surrounding the injury (secondary hyperalgesia).\textsuperscript{18} There is convincing evidence that primary hyperalgesia is caused by sensitization of peripheral receptors and central neurons, whereas secondary hyperalgesia is a result of altered central processing of afferent activity because of sensitization of dorsal horn neurons.\textsuperscript{4,19–25}

The present study sought to counteract the inhibitory effect of ketamine on secondary hyperalgesia by preceding infusion of naloxone.

**Material and Methods**

Twenty-five healthy male volunteers were included in the study. None received any medication for at least 48 h before the study periods. Each participant in the study had been familiarized with the experiment protocol and the extent of the burn injury on a separate day. Informed consent was obtained, as was approval by the local ethics committee and the Danish National Board of Health.

Two subjects were excluded during the study, one because of a psychotomimetic reaction during infusion of study drug, and one because of recurring second-degree burn injuries to the test area.

**Experimental Procedures**

The study was three-way cross-over, double-blind, randomized, and placebo-controlled. According to a computer-generated randomization list, the study drugs were prepared by a certified registered nurse with no other connection to the study. The three treatment regimens were:

1. Injection of naloxone, 0.8 mg/15 min, followed by 0.4 mg/h; 30 min after injection of naloxone, injection of intravenous ketamine 0.5 mg · kg\textsuperscript{-1} · 15 min\textsuperscript{-1} followed by 0.3 mg · kg\textsuperscript{-1} · h\textsuperscript{-1}

2. Injection of normal saline solution followed by infusion of normal saline; 30 min after injection of saline, injection of intravenous ketamine 0.5 mg · kg\textsuperscript{-1} · 15 min\textsuperscript{-1} followed by 0.3 mg · kg\textsuperscript{-1} · h\textsuperscript{-1}

3. Injection of normal saline solution followed by infusion of normal saline; after 30 min, injection of normal saline followed by infusion of saline

**Schedule**

At 0 min, heat-pain detection threshold (HPDT) values were obtained, followed by induction of hyperalgesia.

At 60 min, measurements of HPDT values, areas of secondary hyperalgesia, and sedation were made.

At 75 min, initiation of naloxone-placebo-placebo infusion took place.

At 90 min, measurements of HPDT values, areas of secondary hyperalgesia, and sedation were made.

At 105 min, initiation of ketamine–ketamine–placebo infusion took place.

At 135 min, measurements of HPDT values, areas of secondary hyperalgesia, and sedation were made.

**Heat-pain Detection Thresholds (Thermal Thresholds)**

*Heat-pain detection threshold* was defined as the lowest temperature perceived as painful. A thermode identical to the thermode used for induction of the burn injury was applied to the skin.

Heat-pain detection thresholds were determined by increasing temperature of the thermode from 35°C with a rate of change of 1°C/s, having instructed the subjects to press a button on a device connected to the thermode indicating that the pertinent temperature had been reached. This temperature was registered, and the thermode automatically returned to baseline. A cut-off temperature limit of 52°C was defined, above which the thermode was to return to baseline and a threshold of 52°C would be registered. In no instances was this cut-
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Table 1. Heat Pain Detection Threshold (°C)

<table>
<thead>
<tr>
<th></th>
<th>Naloxone/Ketamine</th>
<th>Placebo/Ketamine</th>
<th>Placebo/Placebo</th>
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</thead>
<tbody>
<tr>
<td><strong>Unburned calf</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>45.8 (44.4–47.7)</td>
<td>46.7 (44.9–48.0)</td>
<td>45.9 (45.3–47.0)</td>
</tr>
<tr>
<td>60 min</td>
<td>46.0 (44.1–46.6)</td>
<td>46.1 (44.5–47.2)</td>
<td>45.9 (44.7–46.9)</td>
</tr>
<tr>
<td>90 min</td>
<td>46.0 (44.6–46.7)</td>
<td>46.0 (44.4–47.1)</td>
<td>45.8 (44.3–46.8)</td>
</tr>
<tr>
<td>135 min</td>
<td>46.7 (45.6–47.5)</td>
<td>43.1 (40.6–46.0)</td>
<td>45.5 (43.9–46.5)</td>
</tr>
<tr>
<td><strong>Burned calf</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>46.6 (44.9–47.9)</td>
<td>46.8 (45.3–48.5)</td>
<td>45.9 (44.4–47.6)</td>
</tr>
<tr>
<td>60 min</td>
<td>41.5 (39.6–45.2)</td>
<td>42.1 (40.3–43.6)</td>
<td>41.1 (39.9–44.1)</td>
</tr>
<tr>
<td>90 min</td>
<td>41.9 (39.3–43.4)</td>
<td>41.6 (39.4–44.6)</td>
<td>40.8 (39.4–42.4)</td>
</tr>
<tr>
<td>135 min</td>
<td>43.0 (39.8–44.6)</td>
<td>43.1 (40.6–46.0)</td>
<td>40.6 (39.5–42.9)</td>
</tr>
</tbody>
</table>

Values are median (quartiles).

A model that has previously proven reliable was used to produce hyperalgesia. A first-degree burn injury was induced in the subjects by heating the medial surface of the right calf (L3-L4 dermatome) with a rectangular thermode measuring 25 × 50 mm (Thermostek, Somedic A/B, Solllentuna, Sweden) strapped to the skin. The borders of the thermode were carefully marked on the skin for subsequent accurate placement of the thermode at the same site. The temperature was 47°C, and heating time was 7 min. One hour after heating the area, primary hyperalgesia in the burned area and a zone of persistent secondary hyperalgesia around the burn injury could be demonstrated, as had previously been shown and had recently been reproduced.

Measurement of Mechanical Hyperalgesia

The temperature of the injured site on the right calf was stabilized at 35°C with the thermode, from 1 min before assessment, and throughout assessment of secondary hyperalgesia. The border area of hyperalgesia was determined by stroking with a brush or by pinpricking the calf along four linear paths arranged radially around the thermal injury. Pinprick was performed with the von Frey technique using a nylon filament with a diameter of 1 mm and a bending force of 1.15 N. Stroke hyperalgesia was induced by gently stroking the calf with a brush made of foam. The stimulation was initiated in an area well outside the area of hyperalgesia and gradually continued toward the area of the burn injury in steps of 5 mm at intervals of 1 s. Immediately after the determinations of hyperalgesia, the thermode was removed.

Assessment of Side Effects

Sedation was assessed on an 11-point numeric scale (0 = completely awake; 10 = almost asleep). Discomfort was assessed on an 11-point numeric scale (0 = no discomfort; 10 = maximal discomfort). Nausea was registered on a four-grade verbal rating scale (none, light, moderate, or severe). Finally, subjects were asked if they experienced hallucinations or any other sensations.

Statistical Analyses

Data are presented as medians (quartiles). Friedman’s analysis of variance has been applied. All significant P values have been corrected, using Bonferroni correction for repeated measurements. Statistically significance was considered to be at P < 0.05.

Before entering statistical analyses, data regarding HPDT and areas of secondary hyperalgesia were normalized to achieve the same point of reference in subjects from all of the three study days.

Results

Primary Hyperalgesia

In all three experimental settings, HPDT inside the burned area on the right calf decreased significantly 60 min after inducing a first-degree burn injury and remained decreased throughout the study (P < 0.05).

Heat-pain detection thresholds did not differ in the subjects regardless of infusion of naloxone or placebo (P = 0.96), nor did the combined effects of placebo followed by placebo, placebo followed by ketamine, or
naloxone followed by ketamine induce any changes in HPDT \( (P = 0.07); \) table 1. Thermal thresholds in the contralateral unburned calf did not differ from a baseline value, regardless of treatment (table 1).

**Secondary Hyperalgesia**

After induction of burn injury, no spontaneous pain or other sensations were experienced from the site of injury. Areas of secondary hyperalgesia toward pinprick or stroking with a brush around the injured area on the right calf were detected easily in all subjects from 60 min after induction of burn injury. Administration of naloxone compared with administration of placebo induced no significant changes in areas of secondary hyperalgesia toward pinprick \( (P = 0.20) \) or toward brush \( (P = 0.48); \) figs. 1 and 2). The ensuing infusion of ketamine, however, was found to reduce the areas of secondary hyperalgesia for both pinprick \( (P < 0.05) \) and stroking \( (P < 0.05) \) on the calf compared with placebo, regardless of preceding naloxone or placebo infusion (figs. 1 and 2). No significant differences in the degree of reduction of secondary hyperalgesia were observed between the two regimens in which ketamine was infused in the area of secondary hyperalgesia using either pinprick \( (P = 0.53) \) or stroke stimuli \( (P = 0.67) \).

**Side Effects**

No sedation was noted when infusing naloxone or placebo. However, when the subsequent infusion of ketamine was initiated, median sedation scores of 4 (quartiles, 2–6) for naloxone–ketamine infusion and 5

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**Fig. 1.** Area of secondary hyperalgesia with pinprick \( (n = 23) \). Medians (quartiles) are shown. White bars = naloxone infusion followed by ketamine infusion; hatched bars = placebo infusion followed by ketamine infusion; black bars = placebo infusion followed by placebo infusion; asterisk = significantly larger area of secondary hyperalgesia in the group not receiving ketamine \( (P < 0.05) \). There was no significant difference between the two groups receiving ketamine.

**Fig. 2.** Area of secondary hyperalgesia with stroking stimuli \( (n = 23) \). Medians (quartiles) are shown. White bars = naloxone infusion followed by ketamine infusion; hatched bars = placebo infusion followed by ketamine infusion; black bars = placebo infusion followed by placebo infusion; asterisk = significantly larger area of secondary hyperalgesia in the group not receiving ketamine \( (P < 0.05) \). There was no significant difference between the two groups receiving ketamine.
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(quartiles, 3-6) for placebo-ketamine infusion were achieved. These scores did not differ \( (P = 0.82) \). The scores, however, proved significantly different from the infusion of placebo-placebo, for which the median sedation score was 0 (quartiles, 0; \( P < 0.05 \)).

In six instances, reports of changed perceptions of body parts were encountered during infusion of ketamine regardless of concomitant infusion of naxalone. No nausea was reported. No other forms of discomfort were noted, and no definite hallucinations were reported.

Discussion

The objective of this study was to investigate to what extent opioid receptor blockade by naxalone could inhibit a well-known clinical response to intravenous injection of ketamine. A prerequisite for the present study was the reproduction of results obtained by Ilkjær et al., showing that infusion of ketamine, \( 0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \), can decrease the secondary hyperalgesia occurring after a first-degree burn injury in humans. These findings have been reproduced.

In the present study, no opioid-mediated effect of ketamine was demonstrated, as the clinical effect of ketamine remained unchanged regardless of concomitant infusion of naxalone. This finding is in line with those of Mauret et al.\textsuperscript{27} that naxalone, 1.6 mg, prevented the analgesic effect of meperidine but had no effect on ketamine analgesia. Our findings, however, contradict animal studies, indicating that there is an effect of ketamine on the opioid receptor.\textsuperscript{10,28}

Regarding the size of our study population, the power of the study is 80\%, given that the smallest reduction of the area of secondary hyperalgesia not to be overlooked would amount to 21\%.

It could be argued that the dose of naxalone chosen was too small. A larger dose might have been required to antagonize any opioid-mediated effect of ketamine. In a study by Brennum et al.,\textsuperscript{17} which investigated the effect of opioids on the secondary hyperalgesia after a first-degree burn injury, the inhibitory effect of 4 mg epidurally injected morphine on this secondary hyperalgesia was antagonized by intravenous injection of naxalone, 0.1 mg/kg. However, Smith et al.\textsuperscript{28} have demonstrated that the in vitro affinity of ketamine to opioid receptors is considerably weaker than other drugs showing primarily opioid receptor antagonism, and as such it should be possible to antagonize effects on the opioid receptor with a relatively smaller dose than that necessary to reverse opioid receptor agonism in a normal clinical setting. It should be noted that the cumulative dose of naxalone given in the present study is the same as that used to reverse heroin-induced coma in drug addicts,\textsuperscript{29} and as such any clinically significant effect of ketamine on the opioid receptors should be antagonized using this dose. Doses similar to or even smaller than those used in the present study have been effective in managing opioid-induced side effects. A dose of 0.8 mg (0.4 mg intravenously and 0.4 mg subcutaneously) has been shown to improve respiratory parameters after high-dose alfentanil anesthesia,\textsuperscript{30} and considerably smaller doses of naxalone have been shown to antagonize pruritus after epidural morphine.\textsuperscript{31}

Apart from studying the effects of naxalone on the well-known effects of ketamine on secondary hyperalgesia, we have investigated the effects of naxalone on ketamine-induced sedation. No difference in sedation scores was found after ketamine infusion, regardless of concomitant naxalone infusion. This finding does not support findings by Stella et al.,\textsuperscript{14} who reported inhibition of the loss of consciousness after injection of ketamine, 0.4 mg/kg, by injection of naxalone, 0.006 mg/kg. Our findings rather support the findings of Hao et al.,\textsuperscript{15} who found that ketamine does not possess any opioid agonistic effect but acts by antagonizing excitatory amino acids. Based on our findings in this experimental setting, the beneficial effects of a combination of opioids and ketamine in controlling acute (postoperative) pain, as observed by Bristow and Orlikowski,\textsuperscript{32} Javery et al.,\textsuperscript{33} and Wong et al.,\textsuperscript{34} may be explained by the different receptors involved and the possibility of acquiring an additive or even a synergistic effect\textsuperscript{35} by combining opioids and NMDA-receptor antagonists. This topic, however, is not fully elucidated yet, as Edwards et al.\textsuperscript{37} failed to demonstrate any improvement in analgesia by adding ketamine to an infusion of morphine, and Ilkjær et al.\textsuperscript{38} were unable to improve postoperative pain control by adding ketamine to a combination of epidural local anesthetics and patient-controlled morphine injections.

Conclusion

Infusion of ketamine can decrease secondary hyperalgesia occurring after a first-degree burn injury in humans. In the present study, this effect was not signifi-
cantly abolished by the concomitant administration of naloxone, although it is possible that some effect of naloxone might have been overlooked because of a type II error.

Sedation observed after administration of ketamine is not affected by naloxone. In this experimental setting, the effect of ketamine on secondary hyperalgesia was not affected by blocking opioid receptors with naloxone.

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