

# Prolonged Analgesic Effect of Ketamine, an *N*-Methyl-D-Aspartate Receptor Inhibitor, in Patients with Chronic Pain

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## ABSTRACT

We examined the role of *N*-methyl-D-aspartate (NMDA) receptors in chronic (pathological) pain in humans by using the NMDA receptor antagonist ketamine as a probe. Thirty patients with neuropathic pain in the trigeminal area were given an i.m. injection of ketamine 0.4 mg/kg combined with midazolam 0.05 mg/kg. Pethidine 1.0 mg/kg served as a control. Three different response patterns were observed. Ketamine caused a long-term (6–24 h) analgesic effect partly dissociated from the mental side effects in 8 of the 26 patients who completed the study; these patients also had a slight analgesic effect of pethidine. In nine patients, ketamine caused a short-lasting (<2 h) analgesic effect closely associated with the mental side effects, whereas pethidine caused little or no analgesia. The remaining nine patients did not experience any reduction of pain after either drug in spite of characteristic side effects. One week after the

i.m. challenge the patients received either 4.0 mg/kg ketamine hydrochloride or placebo capsules to be taken orally as a nightly dose for three consecutive nights. Five of the eight patients who had a long-term analgesic effect of the i.m. challenge reported decreased pain on days after ketamine. None of the others reported an analgesic effect. The phenomenon of long-term depression of pain in a subgroup of patients was thus confirmed when ketamine was given p.o. These findings indicate that NMDA receptors are involved in the perception and maintenance of pathological pain in some patients. In others, pain appears to be mediated by NMDA receptor-independent mechanisms. We suggest that NMDA receptor-independent transmission in central pain pathways may contribute to the reduced efficiency of analgesic drugs often seen in chronic pain states.

Glutamate is a major transmitter in central pain pathways. The excitatory effect of glutamate is mediated by two main types of ionotropic receptors, NMDA (named after the selective agonist *N*-methyl-D-aspartate) and AMPA (named after the selective agonist  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid). The NMDA receptors are Ca<sup>2+</sup> channels that also sustain Na<sup>+</sup> and K<sup>+</sup> currents, whereas AMPA receptors mainly sustain Na<sup>+</sup> currents. It is generally held that the AMPA receptors mediate fast excitatory synaptic transmission. The NMDA receptors contribute to normal excitatory transmission and, in addition, these receptors have special functions related to synaptic plasticity (Collingridge and Singer, 1990; Dickenson et al., 1997). In animal experiments, activation of NMDA receptors in secondary afferent neurons is essential for the increased sensitivity to pain (wind-up) caused by repeated nociceptive stimulation (Davies and Lodge, 1987; Dickenson and Sullivan, 1987). Wind-up is an experimental model for central sensitization, which is regarded as an important mechanism in chronic (pathological) pain. The possibility that NMDA receptor an-

tagonists may be clinically useful in pathological pain states has therefore attracted much attention in recent years (Dickenson, 1990, 1994; Woolf and Thompson, 1991; Coderre et al., 1993).

Ketamine is an NMDA receptor inhibitor that is available for clinical use as a general anesthetic. Ketamine binds to a specific site for phencyclidine (PCP)-like drugs in the NMDA receptor-gated channel and inhibits the excitatory effect of glutamate selectively at these receptors (for review, see Lodge and Johnson, 1990). The PCP site is localized in the NMR1 subunit, which is common to all NMDA receptors, and ketamine inhibits all NMDA receptor subtypes presently cloned. Subanesthetic doses of ketamine effectively attenuates acute nociceptive pain in humans (Domino et al., 1965). This analgesic effect is not blocked by the opioid receptor antagonist naloxone (Maurset et al., 1989). The analgesic effect of ketamine occurs at concentrations within its PCP site occupancy range, and the analgesic potencies of the enantiomers, (*R*)- and (*S*)-ketamine, correlate positively with their respective PCP site binding (Klepstad et al., 1990; Øye et al., 1991). The acute analgesic effect of ketamine in humans is closely associated with mental side effects, including

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**ABBREVIATIONS:** NMDA, *N*-methyl-D-aspartate; AMPA,  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid; PCP, phencyclidine; VAS, visual analog scale.

various disturbances of sensory perception (Øye et al., 1992). Other potent NMDA receptor inhibitors, like dizocilpine and PCP, have similar psychotomimetic effects. Although other pharmacological mechanisms may contribute to the effects of ketamine at high (anesthetic) concentrations (see Meller, 1996), the available evidence favors the hypothesis that its analgesic effect at low subanesthetic doses are related to inhibition of NMDA receptors.

The purpose of the present investigation was to study the role of NMDA receptor-related mechanisms in chronic pain in humans by using ketamine as a pharmacological probe. In particular we wished to test the hypothesis that ketamine may cause a long-term depression of pain in some chronic pain patients (Mathisen et al., 1995). We examined the effect of a single i.m. dose of ketamine using the synthetic opioid pethidine as a control. One week after the i.m. challenge, we tested the effect of ketamine administered p.o. nightly for three consecutive nights.

## Materials and Methods

**Subjects.** Thirty patients (26 women, four men, mean age 57.6 years, range 29–89 years) were recruited from the Department of Maxillofacial Surgery at Ullevål University Hospital in Oslo. All suffered from trigeminal neuropathic pain (secondary trigeminal neuralgia according to the Classification of chronic pain by the International Association for the Study of Pain; Merskey and Bogduk, 1994). In contrast with patients with idiopathic trigeminal neuralgia (tic douloureux) who suffer from bouts of lancinating pain, these patients have constant orofacial pain. Most of the patients in the study related the onset of pain to dental procedures causing nerve damage, such as endodontic treatment, apical surgery, or extractions. The term “phantom tooth pain” has also been used to describe this type of pain (Marbach, 1978). All patients included had unilateral pain with somatosensory disturbances such as mechanical and thermal allodynia, dysesthesia, and hypoesthesia. Patients with temporomandibular joint syndrome, muscular pain, a psychiatric diagnosis, or a pain score below 25 on the visual analog scale (VAS) described below were excluded from the study. The patients went through a medical and dental examination including computer tomography of the head and neck region. Most of the patients had been treated with analgesics, antiepileptics, antidepressants, nerve blocks, and other procedures without or with modest or temporary effects. The mean duration of the painful state was 6 years (range 0.5–20 years).

**Study Design and Drug Administration.** The study followed a double-blind crossover protocol. Patients were randomized in blocks of four according to sex, age, and duration of pain. We evaluated the effects of ketamine administered both i.m. and p.o.. In the first part a dose of 1.0 mg/kg pethidine or 0.4 mg/kg ketamine combined with 0.05 mg/kg midazolam was injected i.m. in a randomized order. One week later the other drug was tested by the same procedure. The doses of ketamine and pethidine were the same as those previously found to be highly effective, reliable, and nearly equianalgesic in patients suffering acute postoperative pain in the same anatomical region (Maurset et al., 1989). Midazolam, which has no analgesic effect by itself, was given together with ketamine to reduce the mental side-effects.

One week after the i.m. challenge, we examined the possibility that ketamine given as a single oral dose at bed-time might work overnight to reduce pain the following day. This part of the study included the 26 patients who had completed the trial of i.m. ketamine versus pethidine. The patients were given either 4 mg/kg ketamine hydrochloride or placebo (lactose) in identical capsules to be taken at bedtime for three consecutive nights using the same randomization as for the i.m. test.

The protocol was acknowledged by the Regional Ethical Committee. Ketamine and pethidine used for i.m. injection were the available commercial preparations Ketalar (Warner Lambert Nordic AB, Solnr, Sweeden) and Pethidine (NycoMed, Oslo, Norway); ketamine hydrochloride used in the capsules was obtained from Norsk Medisinaldepot (Oslo, Norway).

**Assessments.** Pain was assessed by means of a 100-mm vertical VAS (0 = no pain, 100 = intolerable pain) in the morning and in the evening on 3 days before and on 3 days after the i.m. challenge. On the test day, pain was assessed immediately before the injections, every 5 min during the following hour, and hourly for the rest of the day. When ketamine was given orally, pain was assessed in the morning and at bedtime on 3 days before medication, on 3 days during medication and on 3 days after medication.

Side effects were recorded by a standardized questionnaire after each of the trials. The patients assessed their global preference for one of the two treatment alternatives on a horizontal 100-mm VAS that was divided in two equal parts (0 = no difference, 50 mm to the left = maximal preference for the first treatment, 50 mm to the right = maximal preference for the last treatment).

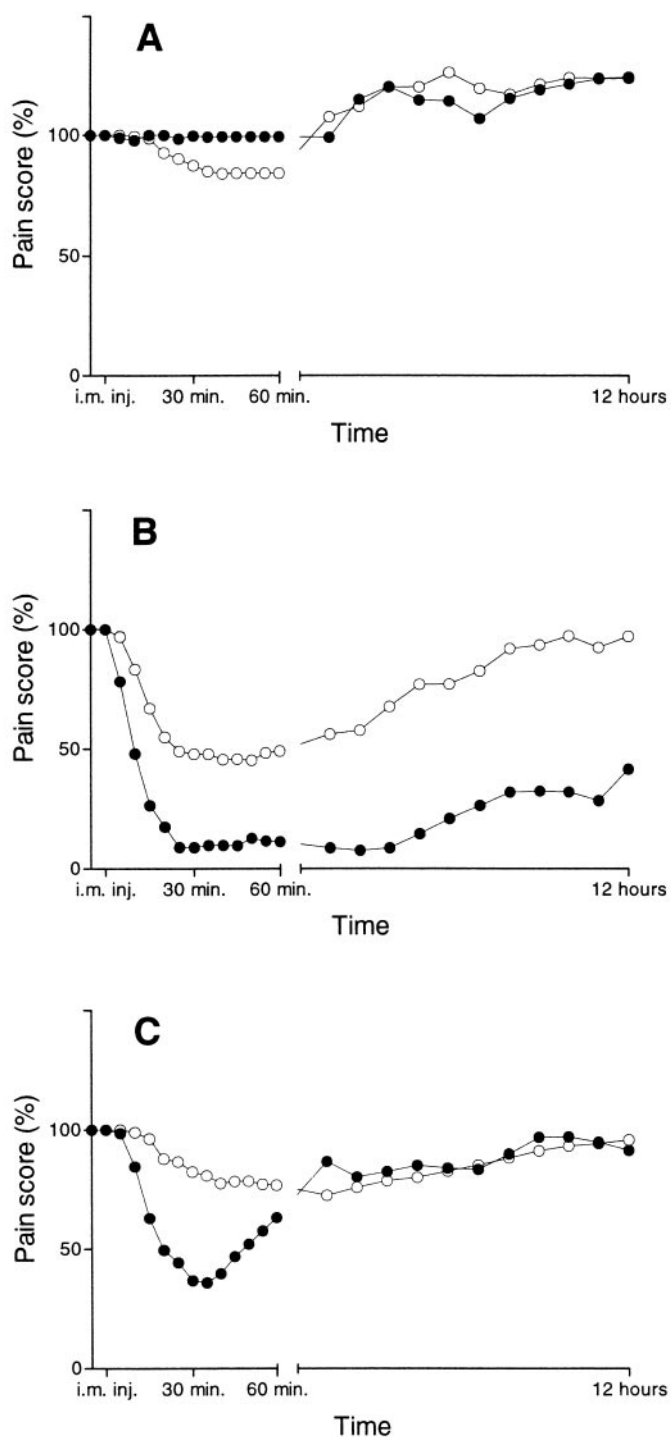
Statistical analysis was performed using a two-sided Wilcoxon signed-rank test to compare mean pain scores (= percentage of baseline pain) after the two treatment alternatives within each of the three groups of patients, and a Mann-Whitney test to compare pain levels, age, and duration of pain between groups. A 5% significance level was applied.

## Results

**i.m. Injections.** Patients with constant neuropathic trigeminal pain did not respond to an analgesic dose of ketamine or pethidine in a uniform way. Nine patients did not experience a reduction in pain after either of the two drugs (Fig. 1A). Eight patients reported an analgesic effect that lasted for many hours after injection of ketamine. These patients also had a small but significant analgesic effect from pethidine (Fig. 1B). Nine patients reported a short-lasting pain reduction after the injection of ketamine, but felt little pain relief after pethidine (Fig. 1C). Four patients withdrew from the trial, three because of nausea after pethidine injection and one from reasons unrelated to the drugs given. Mean age and duration of pain in the three groups of patients are shown in Table 1.

The most common side-effects of both drugs were dizziness, sedation, and dry mouth (Table 2). Sensory disturbances, in particular blurred vision and altered hearing, as well as a general feeling of insobriety, were more frequent and more severe after ketamine. Six patients reported sensory illusions after ketamine. The side effects of ketamine occurred in all three groups of patients and lasted for less than 1 h. The patients also evaluated their relative preference for one of the two drugs, taking both pain relief and side effects into account. Five of the nine patients in the nonresponder group preferred pethidine to ketamine, three had no preference, and one preferred ketamine (Fig. 2A). Of the eight patients with a long-lasting analgesic effect of ketamine, six preferred ketamine, one had no preference, and one preferred pethidine (Fig. 2B). Four of the patients who had a transient or partly transient pain reduction after ketamine had no preference for either of the two drugs, three preferred ketamine and two preferred pethidine (Fig. 2C).

**Oral Administration.** One week after the i.m. challenge we examined the effect of ketamine taken orally at night by the 26 patients who completed the first part of the study. Five



**Fig. 1.** Pain score [pain in percentage of baseline as registered by use of a VAS (0 = no pain, 100 = intolerable pain)] after an i.m. injection of ketamine (●) and pethidine (○). Recordings were made before injection (baseline), every 5 min for 1 h, and then hourly for the next 12 h. A, mean pain scores of nine patients without analgesic effect after i.m. ketamine. At 30 min these patients scored on average 99.7% of baseline (S.D., 0.8; range, 97.5–100) after ketamine and 87.4% (S.D., 19.3; range, 40–100) after pethidine. There was no statistically significant difference between ketamine and pethidine effects on pain scores at 30 min. However, pethidine as compared with baseline pain gave a minor but significant pain reduction ( $p < .05$ ). At 60 min, mean pain score was 99.4% (S.D., 1.8; range, 94.7–100) after ketamine and 84.3% (S.D., 22.8; range, 40–100) after pethidine. B, mean pain scores of eight patients with long-term analgesic effects after i.m. ketamine. At 30 min mean pain score for this group was 9.0% of baseline (S.D., 20.9; range, .0–60) after ketamine and 47.7% (S.D., 34.5; range, 7.4–97.6) after pethidine. At 60 min, pain score

of the eight patients who reported a long-term depression of pain after the i.m. challenge also reported pain relief on days after taking ketamine p.o. at night. None of the patients without a prolonged analgesic response to the i.m. challenge reported decreased pain intensity on days after oral ketamine (Fig. 3). The mean initial pain assessment appeared to be slightly lower in the patients who were ketamine responders, but the difference was not statistically significant. The reported pain relief in the ketamine responders varied greatly between the patients, but the characteristic response of each patient remained constant throughout the 3-day test period. Two examples of VAS recordings after oral ketamine are presented (Fig. 4). These two examples represent the most (Fig. 4A) and least pronounced (Fig. 4B) analgesic effect in these patients. The mental side effects after oral ketamine were qualitatively similar, but lasted longer and were more pronounced than the side effects seen after ketamine given parenterally in combination with midazolam. However, side effects were only reported by patients who did not fall asleep during the first 20 to 30 min after taking ketamine. Some patients reported that ketamine improved their sleep. None reported hangover the following morning.

Three of the five patients with pain relief after oral ketamine preferred ketamine to placebo, two had no definite preference. These two patients had disturbing mental side effects after the oral dose of ketamine. Also, two of the patients who preferred ketamine to placebo reported mental side effects.

## Discussion

The analgesic effect of ketamine in patients suffering chronic orofacial pain is strikingly different from the effect reported previously in acute nociceptive pain. In a recent study, all patients with acute postoperative orofacial pain ( $n = 20$ ) experienced an analgesic effect that lasted for less than 1 h after an i.m. injection of ketamine, whereas patients with chronic orofacial pain ( $n = 7$ ) either reported a long-

was 11.3% (S.D., 9.7; range, .0–20.2) after ketamine and 49.0% (S.D., 26.2; range, 5.4–97.6) after pethidine. Two hours after drug injections, pain scores were 9.8% (S.D., 8.5; range, .0–21.2) and 56.0% (S.D., 34.4; range, 5.4–102.1) for ketamine and pethidine respectively. After 3 h, the scores after ketamine were on average 8.7% (S.D., 7.0; range, .0–20) of baseline and after pethidine 57.6% (S.D., 35.1; range, 5.4–108.5). Six and twelve hours after the injection of ketamine, mean pain level was still reduced; pain scores were 23.8% (S.D., 22.3; range, 4.44–70) and 47.3% (S.D., 49.3; range, .0–140.3), respectively. At all registrations after the ketamine injection, pain scores were significantly different from baseline pain ( $p < .02$  for all except at 12 h;  $p < .05$ ). After the pethidine injection, mean pain scores were significantly different from baseline pain for the first 4 h ( $p < .02$  until 2 h,  $p < .03$  at 3 h, and  $p < .04$  at 4 h). The effects of ketamine and pethidine were significantly different at 30 and 60 min, 2, 3, 4, 5, and 12 h ( $p < .03$ ). C, mean pain scores of nine patients with short-lasting analgesic effects after i.m. ketamine. At 30 min, mean pain score was 36.7% (S.D., 33.6; range, .0–78.6) after ketamine and 82.5% (S.D., 16.7; range, 59.5–100) after pethidine. At 60 min, mean pain score was 63.2% (S.D., 24.3; range, 24.3–102) after ketamine and 76.9% (S.D., 21.9; range, 43.2–100) after pethidine. Two hours after drug injections, pain scores were 86.7% (S.D., 15.2; range, 61–103.9) and 72.53% (S.D., 27.1; range, 27.9–100) for ketamine and pethidine respectively. The difference in pain score after the ketamine injection was statistically significant only at 30 ( $p < .01$ ) and 60 min ( $p < .02$ ) and at 2 h ( $p < .04$ ). Correspondingly, pain scores differed from baseline pain at 30 and 60 min ( $p < .03$ ) and at 2 ( $p < .03$ ) and 3 h ( $p < .05$ , mean 75.9%, S.D. 31.1, range 29.1–114.5) after the pethidine injection. Ketamine and pethidine had statistically significantly different effects on the continuous pain at 30 min ( $p < .01$ ) and at 2 h ( $p < .05$ ) after injections.

TABLE 1

Mean patient age and duration of the continuous chronic pain in the three groups of patients

	No Analgesic Effect from Ketamine i.m. (n = 9)	Long-Term Analgesic Effect from Ketamine i.m. (n = 8)	Short-Lasting Analgesic Effect from Ketamine i.m. (n = 9)
Patient age; mean (range)	57.1 years (31–74)	53.8 years (29–74)	59.7 years (35–89)
Pain duration; mean (range)	6.5 years (0.5–11)	4.0 years (0.5–12)	6.4 years (0.5–20)

TABLE 2

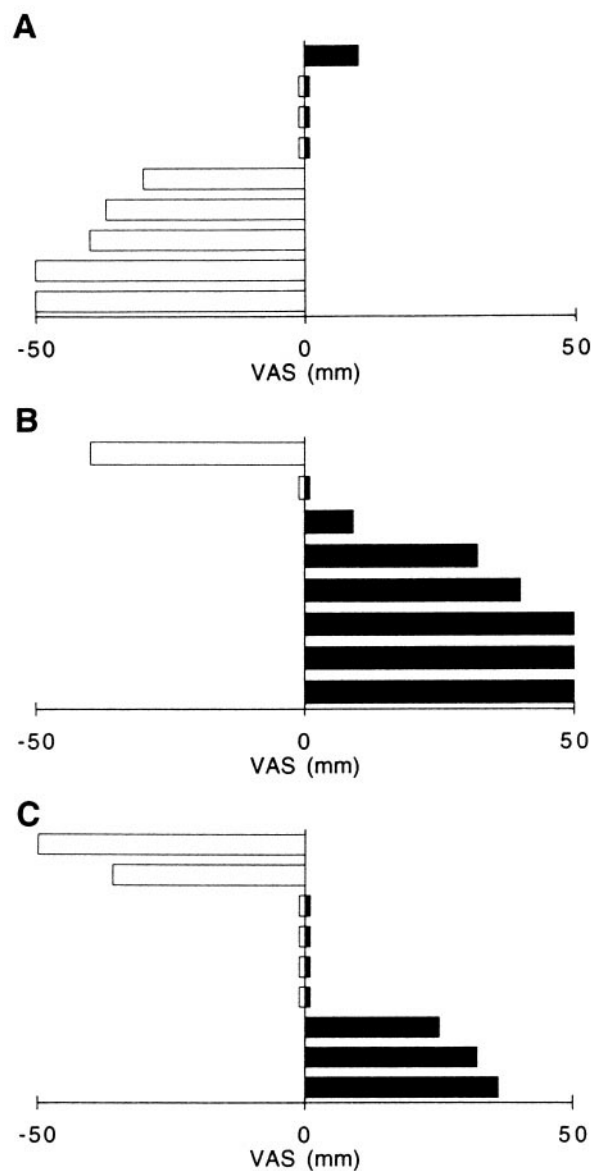
Side effects after i.m. injection of ketamine + midazolam and pethidine

Side Effects	Pethidine	Ketamine + Midazolam
	%	%
Nausea	19.2 (5/26)	7.7 (2/26)
Dizziness	65.4 (17/26)	69.2 (18/26)
Sedation	53.8 (14/26)	69.2 (18/26)
Blurred vision	19.2 (5/26)	61.5 (16/26)
Altered hearing	3.8 (1/26)	15.4 (4/26)
Xerostomia	65.4 (17/26)	61.5 (16/26)
Feeling of insobriety	46.1 (12/26)	96.1 (25/26)
Hallucinations	0.0 (0/26)	23.1 (6/26)

term depression of pain intensity or no analgesic effect at all (Mathisen et al., 1995). The present double-blind crossover study of a new group of 30 patients with trigeminal neuropathic pain provides evidence for the existence of three qualitatively different patterns of response to a subanesthetic dose of ketamine. In the present investigation, eight of the 26 patients who completed the study reported a long-term depression of pain intensity after a single dose, nine patients reported a short-lasting analgesic effect associated with the intoxicating effect of ketamine and nine reported no analgesic effect. This difference in response between individuals was present in spite of efforts to secure a clinically homogeneous group of chronic pain patients.

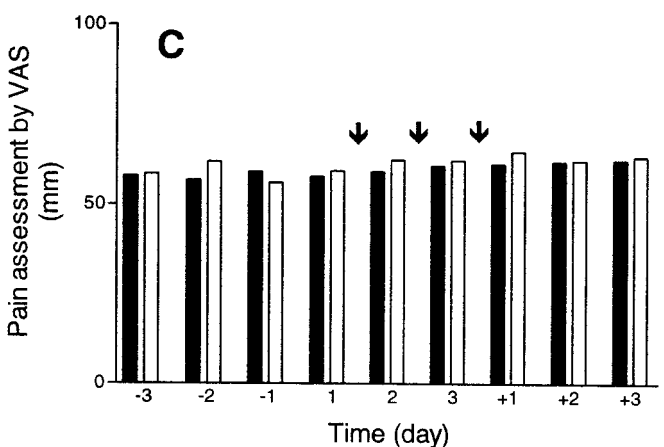
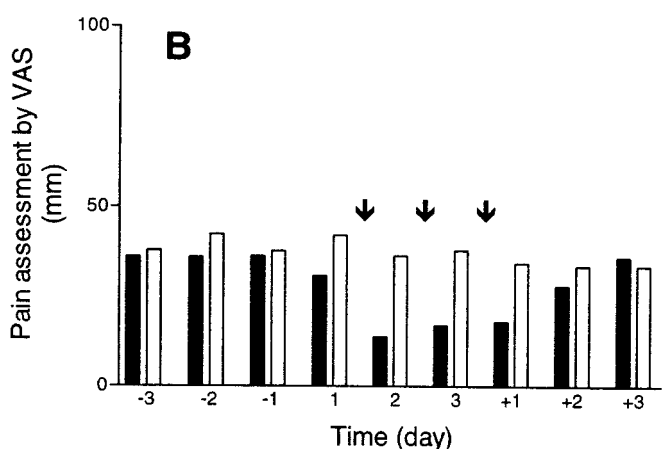
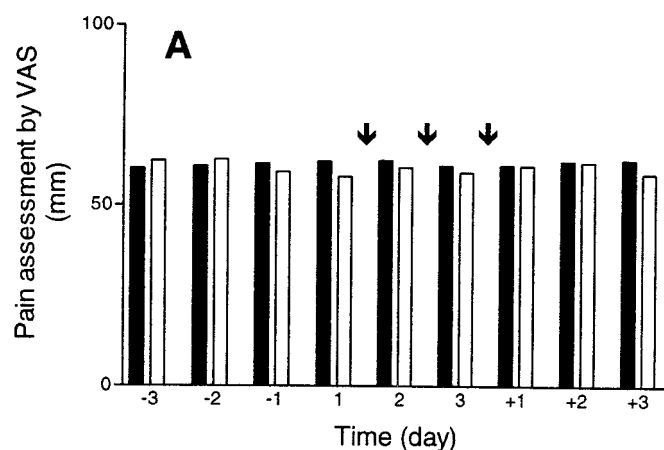
Patients with trigeminal neuropathic pain usually have little pain relief from opiates in low analgesic doses. In the present study a small analgesic effect of 1 mg/kg pethidine was present in the same eight patients who responded to ketamine with a long-term reduction of pain. However, 0.4 mg/kg ketamine was significantly more effective as an analgesic than 1 mg/kg pethidine in these patients. In a previous study of patients with acute postoperative orofacial pain, these doses of pethidine and ketamine were found to be nearly equianalgesic (Maurset et al., 1989). In acute pain, the analgesic effect lasted for less than 30 min after ketamine and for 1 to 2 h after pethidine, reflecting the pharmacokinetic properties of the two drugs. In the present study, the relative duration of the analgesic response to the two drugs was reversed. The analgesic effect of ketamine, which has the shortest pharmacological half-life, lasted significantly longer than that of pethidine. Long-term analgesia after a single analgesic dose of ketamine has also been observed in patients suffering postherpetic pain (Hoffmann et al., 1994; Klepstad and Borchgrevink, 1997), post-traumatic pain (Øye et al., 1996), and fibromyalgia (Sørensen et al., 1997).

The finding that ketamine may cause a long-term depression of pain intensity in some patients with chronic pain supports the hypothesis that NMDA receptor-mediated sensitization may contribute to pathological pain in humans. It is tempting to speculate that inhibition of NMDA receptors by ketamine even for a short time period might serve to annul the sensitization and thereby cause pain relief that

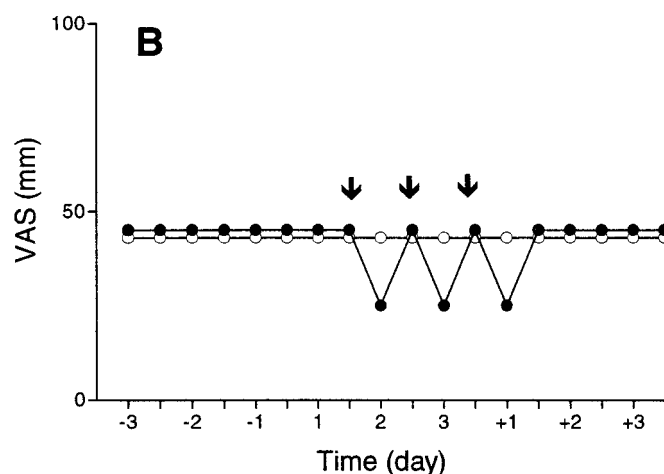
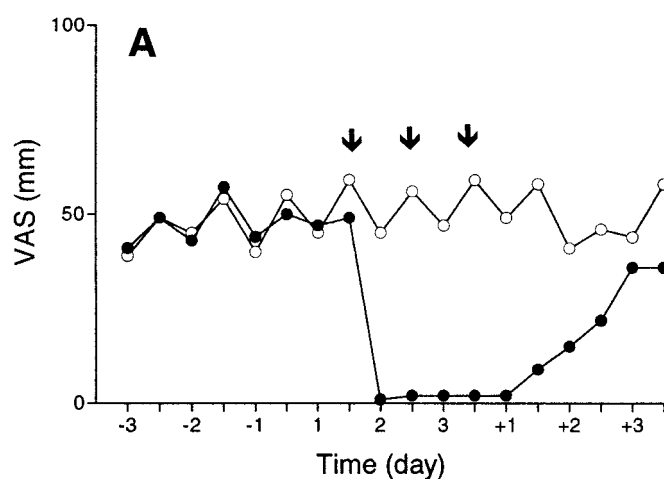


**Fig. 2.** Global preferences expressed on a VAS (0 = no preference to either drug, 50 mm to the right = maximal preference ketamine, 50 mm to the left = maximal preference pethidine). A, global patient preferences in patients without analgesic effect from i.m. ketamine. The global patient preferences represents an overall evaluation of the two drugs, and five of nine patients in this group of nonresponders preferred pethidine, three could not differentiate between the drugs, and one preferred ketamine. B, global patient preferences in patients with long-term analgesic effects from i.m. ketamine. The majority (6/8) of the patients in this group preferred ketamine in spite of the mental side effects. One patient made no preference and one preferred pethidine. C, global patient preferences in patients with a short-lasting analgesic effect after i.m. ketamine. Three patients in this group preferred ketamine, four had no preference, and two patients preferred the pethidine injection.

persists after ketamine has been eliminated from the body. In the present study, re-kindling of the pathological pain apparently occurred during the subsequent 6 to 24 h.



**Fig. 3.** Pain assessment by a 100-mm VAS (0 = no pain, 100 = intolerable pain) before and after oral ketamine (shaded columns) and placebo (open columns). Recordings were made by the patients in the morning on 3 days before (day -3, -2, and -1), during medication (days 1, 2, and 3), and 3 days afterwards (days +1, +2, and +3). Arrows indicate administration of ketamine or placebo capsules. A, mean pain assessments by the six patients who did not respond to the i.m. challenge. There was no statistically significant difference between pain levels after oral ketamine and placebo. B, mean pain assessments by the seven patients who had a long-term analgesic effect i.m. ketamine. Pain levels after oral ketamine were significantly different from placebo on days 2 and 3 ( $p < .05$ ). C, mean pain assessments by the six patients who had a short-



**Fig. 4.** Examples of pain registrations in two patients with analgesic effects on days after a single nightly oral dose of ketamine. The curves show pain levels on a 100-mm VAS (0 = no pain, 100 = intolerable pain) in the morning and at night on 3 days before (days -3, -2, and -1), during (days 1, 2, and 3), and 3 days after (days +1, +2, and +3) oral ketamine (●) and placebo (○). Arrows indicate administration of ketamine or placebo capsules. A, patient experienced a dramatic reduction of pain intensity on the following day and this effect lasted for at least 24 h. B, patient experienced a reduced pain level in the morning, but pain returned during the day.

About one-third of the patients in the present study had a short-lasting effect of ketamine and virtually no effect of pethidine. As an explanation, we suggest that a more complete and apparently irreversible sensitization of NMDA receptors had taken place. In this situation, pain is relieved by ketamine only when present in concentrations sufficiently high to block the NMDA receptor-gated channel. When NMDA receptors are maximally sensitized, other excitatory mechanisms may not be necessary for NMDA receptor activation, and opioids and other drugs that interfere with these excitatory mechanisms have little or no effect.

lasting analgesic effect after i.m. ketamine. There was no statistically significant difference between pain levels after oral ketamine and placebo.

The fact that both ketamine and opiates were unable to suppress pain in nine of the 26 patients in the present study indicates that chronic pain, in contrast to acute pain, may be mediated mainly by NMDA receptor-independent pathways in some patients. This finding does not support the paradigm of NMDA receptor-mediated sensitization as a universal mechanism of neuropathic pain. Possibly, a transition from NMDA to nonNMDA receptor-mediated transmission in central pain pathways may be responsible for the reduced efficiency of analgesic drugs often seen in pathological pain states. The present study does not serve to elucidate whether the three different patterns of response represent different stages in chronic pain development or three pharmacologically separate types of chronic pain. There was no significant difference in age or duration of the painful state between the patients in the three response groups.

A temporal dissociation between analgesia and mental side effects in some patients may have clinical implications for the use of ketamine and other NMDA receptor-blocking agents in the treatment of chronic pain. In the second part of the study we tested the possibility that ketamine may work during sleep to reduce pain the following day, and that the psychotomimetic side effects might be reduced or avoided by this mode of administration. We chose to give ketamine p.o. because of the obvious advantages of oral administration in the treatment of chronic pain. We are aware that nightly injections of ketamine might possibly better serve the purpose of testing the hypothesis. However, the results of the present study confirm our previous observations that ketamine given as a single nightly dose may reduce pain intensity the following day in some patients with chronic pain (Øye et al., 1996). Only five of the 26 patients experienced reduced pain intensity on days after oral ketamine. These patients belonged to the group of eight patients who reported a long-term pain depression after i.m. ketamine. The phenomenon of long-term depression of pain in a subgroup of patients was thus confirmed when ketamine was given p.o. at night.

The bioavailability of ketamine given p.o. has been reported to be about 15% (Grant et al., 1981). Most of the ketamine given orally is rapidly metabolized to norketamine. Norketamine is also an NMDA receptor inhibitor, but the  $IC_{50}$  is about 10 times higher than for ketamine (I. Øye, unpublished studies). Accordingly, the doses used in the present study were 4 mg/kg p.o. compared with 0.4 mg/kg parenterally.

Like the analgesic effect, the psychopharmacological effect of ketamine is highly variable between patients, being quite dramatic in some and almost absent in others. The most frequent mental side effects are sensory illusions and dysperceptions, which is consistent with the idea that NMDA receptors are generally involved in sensory perception (Øye et al., 1991, 1992). The mental side effects occurred independently of an analgesic action and lasted for less than 1 h after i.m. injection, reflecting the rapid brain kinetics of ketamine (Hartvig et al., 1995). However, ketamine may induce disease-related symptoms in schizophrenic patients (Lahti et al., 1995), and these symptoms may last for longer time periods. It is a clinical experience that the psychotomimetic effects most often occurs in anxious and apprehensive individuals and that these effects are inhibited by benzodiazepines given before, but not after, ketamine. Quiet surroundings and a relaxed and confident atmosphere also contribute

to reduce the side effects. Ketamine binds to NMDA receptors mainly when the channel is in an activated or open state. It is tempting to suggest that the activity dependence of the mental side effects reflects this pharmacological mechanism.

In the present investigation, the combination of ketamine with a low dose midazolam did not completely abolish the mental side effects. In spite of slight but characteristic side effects, six of eight patients with a long-term analgesic effect preferred ketamine to pethidine. On the other hand, eight of nine patients who did not experience an analgesic effect preferred pethidine or had no global preference.

In conclusion, we observed three different patterns of response to the NMDA receptor blocker ketamine in patients with trigeminal neuropathic pain. Apparently chronic pain in humans may be related to NMDA receptor-dependent mechanisms in some patients and to NMDA receptor-independent mechanisms in others. The possibility that a transition from NMDA receptor-dependent to NMDA receptor-independent mechanisms may be responsible for the loss of sensitivity to analgesic drugs in pathological pain states warrants further investigations.

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