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Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain

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Summary We examined the analgesic effect of racemic ketamine and its 2 enantiomers in 16 female patients (age: 20–29 years) suffering acute pain after oral surgery and in 7 female patients (age: 42–79 years) suffering chronic neuropathic orofacial pain. All 3 forms of ketamine consistently relieved postoperative pain, (S)-ketamine being 4 times more potent than (R)-ketamine. The analgesic effect was maximal 5 min after i.m. injection and lasted for about 30 min. The 7 patients with neuropathic pain received ketamine at one or several occasions. Four patients (age: 54–79 years) who had suffered pain for more than 5 years did not experience an analgesic effect, whereas 3 patients (age: 42–53 years) who had suffered pain for less than 3 years reported pain relief lasting from 24 h to 3 days. The individual type of response did not depend on the form of ketamine used. The mental side effects were qualitatively similar for the 3 forms of ketamine. Relative to the analgesic effect (S)-ketamine caused more disturbing side effects than did (R)-ketamine.

The mean serum concentration of each form of ketamine at the time of maximal effect was close to the approximate K_d value for PCP site occupancy by that particular form. This is in concert with the hypothesis that the effect of ketamine on acute nociceptive pain is due to *N*-methyl-D-aspartate (NMDA) receptor inhibition and adds to the evidence that NMDA receptors are important for the perception of acute, nociceptive pain in humans. The lack of analgesic effect of ketamine in patients who had suffered neuropathic pain for several years shows that NMDA receptors are not involved in the perception of all types of pain and indicates that NMDA receptors become less important for pain perception in older patients with a long pain history. The atypical (prolonged) analgesic effect of ketamine in patients who had suffered neuropathic pain for less than 3 years may be a placebo effect, but the possibility that this effect reflects a permissive role of NMDA receptors during the development of neuropathic pain cannot be excluded.

Key words: Ketamine; Orofacial pain; Neuropathic pain; *N*-methyl-D-aspartic acid; *N*-methyl-D-aspartic acid receptor

Introduction

Ketamine is a phencyclidine-like drug which has been in clinical use as an anesthetic for more than 25 years. Ketamine binds specifically to the phencyclidine site (PCP site) of the *N*-methyl-D-aspartate (NMDA) receptor-gated ion channel and blocks NMDA receptors non-competitively in a use-dependent manner (for review see Lodge and Johnson 1990). The affinity of ketamine for the PCP site is low ($K_d \sim 1$ μM) compared to that of dizocilpine (MK-801) which often is used in vitro and in experimental animals and which has an K_d of ~ 4 nM. Therefore other pharmacological mechanisms, in particular interaction with opiate receptors and *sigma*-sites have been thought to contribute to the clinical effects of ketamine (for example see Reich and Silvay 1989; Lipton and Rosenberg 1994).

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It is well known that ketamine in subanesthetic concentrations inhibits acute nociceptive pain in humans. We have previously found that this effect is non-opioid (Maurset et al. 1989) and correlates positively to PCP site binding (Klepstad et al. 1990). The analgesic effect of ketamine is closely associated with general disturbances of sensory perception (Øye et al. 1992). Distorted sensory perception is characteristic for the 'psychic side effects' of many other NMDA receptor inhibitors, and the clinical manifestation of these dysperceptions is consistent with the idea that NMDA receptors are involved in the cognitive interpretation of afferent sensory signals (Øye et al. 1991).

In animal experiments NMDA receptor antagonists inhibit central sensitization to nociceptive stimuli and nociceptive reactions associated with neuropathic pain rather than the nociceptive reflexes (for examples see Dickenson 1990; Dray et al. 1994). The putative use of NMDA receptor blockers in neuropathic pain syndromes has therefore attracted much interest recently. Ketamine has been reported to relieve neuropathic pain in some patients, but the psychic side effects limit the use of ketamine in patients suffering chronic pain (Stannard and Porter 1993; Backonja et al. 1994).

In the present study we compared the effect of ketamine in patients suffering acute nociceptive orofacial pain with its effect in patients suffering chronic neuropathic orofacial pain. We used both racemic ketamine and the pure enantiomers (R)- and (S)-ketamine in order to examine putative differences in the psychic side effects relative to their analgesic actions.

Methods

Acute orofacial pain

Sixteen healthy women aged 20–30 years had their 3rd molar teeth surgically removed on prophylactic indications, under local anesthesia without premedication. After postoperative pain had developed, the patients were seated comfortably and instructed to record the pain intensity every 5 min on a 100-mm vertical visual analogue scale (VAS, no pain = 0, intolerable pain = 100 mm). When the pain had reached a constant level, the patients received ketamine by intramuscular (i.m.) injection. The patients with bilaterally impacted molars (n = 9) were operated on two occasions at least 1 week apart. These patients received (R)-ketamine on one occasion and (S)-ketamine on the other in a double-blind, randomized order. Patients with unilaterally impacted teeth (n = 7) were given racemic ketamine. The protocol was approved by the Regional Ethical Committee and informed consent was obtained from all participants.

Chronic orofacial pain

Seven female patients aged 42–79 years who suffered severe chronic orofacial pain and who frequently visited the pain clinic at Ullevål Hospital (the Oslo City Hospital) participated in the study. The pain had been diagnosed as neuropathic pain due to nerve damage in the trigeminal region. Clinical and laboratory tests, including CT were negative. Treatments with analgesics, antiepileptics, antidepressants and nerve blocks with local anesthetics had been tried without or with modest effect. The reasons for trying ketamine and the possible psychic side effects were explained to each patient. The patients were free to withdraw from the treatment at any time. The various forms of ketamine were given on an individual basis, either i.m. or intravenously (i.v.) as a single dose sometimes followed by continuous infusion. The patients recorded their pain on the VAS described above and the treatment goal was to obtain analgesia for a time period of at least 15 min. This study was regarded as a pilot investigation. It was not blinded, placebo was not included, and the age of patients did not match that of the patients with postoperative orofacial pain.

Side effects

Side effects were recorded using a slightly modified version of the questionnaire described previously (Klepstad et al. 1990). If the side effects were experienced as highly unpleasant, a hypnotic i.v. dose of midazolam was given.

Serum concentrations of ketamine

The concentration of ketamine in blood serum was assayed by HPLC using an adaption of the method provided by Varian (California) for the use of Bond Elut Certify™ solid-phase extraction columns for the determination of phencyclidine in blood by gas chromatography. A 2-ml serum sample is diluted with 2 ml of 0.1 M sodium acetate buffer, pH 6.0, and 20 μl of 10^{-4} M MK-801 is added as internal standard. The 3-ml Bond Elut Certify™ is conditioned with methanol followed by the same buffer as used for the sample dilution. The column is then rinsed with 1 ml of 1 M acetic acid followed by 6 ml of methanol. Ketamine is eluted with 2 ml of 2% ammonium hydroxide in ethylacetate and the sample concentrated under a stream of nitrogen at 30–40°C. When the sample volume is reduced to about 0.5 ml, 25 μl of 0.1 N HCl is added to produce the HCL salt of ketamine. Evaporation continues until just a film of liquid remains. Then 50 μl of water is added. A 10-μl aliquot is injected on a Waters Nova-Pak™, C_{18}, 4 μm, 3.9×150 mm analytical column. The eluent used is 0.1 M potassium phosphate buffer, pH 3.0, with 22% acetonitrile, flow rate 0.5 ml/min. UV absorption of the eluate is detected by monitoring at 215 nm.

Preparation of ketamine isomers

Racemic ketamine was obtained from Industrial Kern Espanola, Barcelona, Spain, and the enantiomers resolved as described previously (Øye et al. 1992). The enantiomers were dissolved in 0.9% sterile NaCl, the concentrations used were 10 mg/ml for (S)-ketamine and 50 mg/ml for (R)-ketamine. The racemic ketamine used was a commercial pharmaceutical preparation (Ketalar®, Parke-Davis, 50 mg/ml).

Results

Acute postoperative (nociceptive) orofacial pain

Both racemic ketamine and the pure enantiomers (R)- and (S)-ketamine rapidly relieved pain in all subjects. In these patients the drugs were given by i.m. injection and the doses were 0.45 mg/kg for (S)-ketamine, 1.80 mg/kg for (R)-ketamine and 0.80 mg/kg for racemic ketamine. These doses were based on a previous study of the dose–response relationship of the two chiral forms of ketamine (Øye et al. 1992). The time course of the analgesic effect after i.m. injection of the 3 forms is shown in Fig. 1. In the figure, the

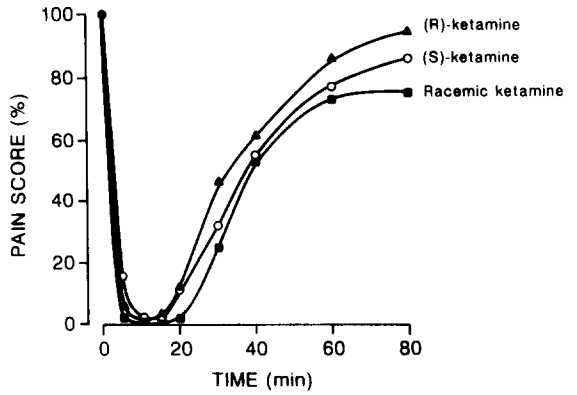

Fig. 1. Effect of racemic ketamine (0.9 mg/kg), (S)-ketamine (0.45 mg/kg) and (R)-ketamine (1.8 mg/kg) on postoperative pain. The figure shows pain score in percent, 100% being the pain assessed by each individual patient on the visual analogue scale in the control period before the drugs were given. Each point represents mean values of seven subjects for racemic ketamine and nine subjects for each of the enantiomers.

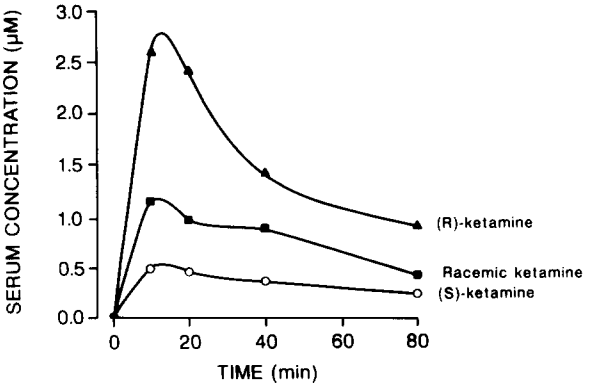

Fig. 2. Serum concentrations of the three forms of ketamine after i.m. injection of 0.9 mg/kg racemic ketamine, 1.8 mg/kg (R)-ketamine and 0.45 mg/kg (S)-ketamine. Each point is the mean value for seven subjects for racemic ketamine and nine subjects for each of the two enantiomers.

analgesic effect is expressed as percent reduction in pain score, 100% being the pain assessed on the VAS before injection of ketamine. Fig. 2 shows the concentration of the 3 forms of ketamine in the blood after i.m. injection. No major difference in the pharmacokinetic properties of the 3 forms of ketamine was found.

Blurred vision and a general feeling of insobriety were the most consistent side effects. Auditory, visual and somatosensory dysperceptions also occurred. The relative frequency of side effects after (R)-, (S)- and racemic ketamine in the patients with acute postoperative pain is shown in Table I. As seen from the table, the number of side effects reported after racemic ketamine and (S)-ketamine was slightly higher than after (R)-ketamine. In addition, the mental effects of (R)-ketamine appeared to be less disturbing than those of (S)-ketamine and racemic ketamine. Dreams and hallucinations were reported by test persons receiving racemic ketamine, but not by any of the persons who received the pure enantiomers.

Chronic (neuropathic) orofacial pain

In contrast to patients with postoperative pain, patients who had an established diagnosis of neuropathic pain in the region of the trigeminal nerve, responded to ketamine in an apparently unpredictable way. These patients were therefore given various doses of ketamine (racemic ketamine, (R)-ketamine or (S)-ketamine) with the therapeutic goal of obtaining a pain-free period of at least 15 min. Of the 7 patients (age: 47–79 years), the 4 oldest (age: 57–79 years) had suffered pain for more than 5 years. Subanesthetic doses of ketamine were without analgesic effect in 3 of these 4 patients. The lack of analgesic effect persisted when the doses of ketamine were increased to near anesthetic levels. One of these patients reported pain relief during the ketamine infusion. The pain returned a few minutes after the infusion was terminated. On the other hand, 3 patients (age: 43–53 years) who had suffered pain for less than 3 years, consistently reported prolonged pain relief after subanesthetic doses of ketamine. The analgesic effect in these patients lasted for more than 12 h. Thus the time course of the

TABLE I

SIDE EFFECTS

The total number of side effects reported by 9 patients receiving (R)- and (S)-ketamine and 7 patients receiving the racemic solution.

Side effect	(S)-ketamine (0.45 mg/kg, i.m.)	(R)-ketamine (1.8 mg/kg, i.m.)	Racemic solution (0.9 mg/kg, i.m.)
Blurred vision	100% (9/9)	78% (7/9)	85% (6/7)
Altered hearing	78% (7/9)	67% (6/9)	57% (4/7)
Dizziness	89% (8/9)	89% (8/9)	100% (7/7)
Proprioceptive disturbances	100% (9/9)	56% (5/9)	71% (5/7)
Illusions	56% (5/9)	22% (2/9)	57% (4/7)
Sedation	0% (0/9)	0% (0/9)	0% (0/7)
Dreams	0% (0/9)	0% (0/9)	43% (3/7)
Hallucinations	0% (0/9)	0% (0/9)	43% (3/7)

TABLE II

EFFECT OF KETAMINE IN 7 FEMALE PATIENTS SUFFERING CONSTANT NEUROPATHIC OROFACIAL PAIN

Patient	Age (years)	Pain history (years)	Trials (n)	Results
1	53	1	2	Pain-free 1–3 days
2	42	2	1	Pain-free 1 day
3	42	3	1	Pain-free 1 day
4	54	5	1	No effect
5	69	11	5	No effect
6	57	12	5	No effect
7	79	21	1	No effect

analgesic effect in some of the patients with neuropathic pain differed distinctly from that found in patients suffering acute postoperative pain. The results are summarized in Table II.

The side effects of ketamine in the patients with neuropathic pain syndromes were similar to those reported by the patients suffering postoperative pain and lasted for about 30 min after i.m. injection or termination of infusion. The patients with chronic pain, however, were more concerned about the side effects, and for this reason some of them received ketamine only once. Therefore a systematic comparison of the 3 types of ketamine was not carried out in this group.

Case histories of the patients with chronic orofacial pain

Patient 1. In this 53-year-old woman pain started spontaneously in 1991. She described her pain as a constant, deep, dull ache radiating from the first left mandibular premolar. Hyperalgesia, allodynia and paresthesia were present. On the first treatment with ketamine she received 0.9 mg/kg racemic ketamine i.m. On the second treatment she received 0.4 mg/kg (S)-ketamine as an i.v. bolus followed by continuous infusion of 22 mg during 30 min. She reported a pain-free period of 2–3 days after the first treatment and 1 day after the second treatment.

Patient 2. In this 42-year-old woman pain started in 1990 in the first premolar of the left maxilla. She described her pain as constant. Paresthesia, hyperalgesia and allodynia were present. She was given 1.8 mg/kg racemic ketamine as a slow i.v. injection. She reported a pain-free period of 1 day.

Patient 3. This 42-year-old woman suffered dental pain localized to the left maxilla since 1989. All premolars and molars were treated endodontically, later with apical surgery and eventually extraction. These procedures did not affect her pain, on the contrary she reported that the pain increased. Paresthesia, hyperalgesia and allodynia was present. She received 0.4 mg/kg (S)-ketamine i.v. The treatment resulted in a pain-free period of 1 day.

Patient 4. This 54-year-old woman suffered facial pain that was diagnosed as temporomandibular joint dysfunction due to malocclusion. In 1987 a mandibular osteotomy was performed to correct the occlusion. This procedure caused nerve damage to the left mandibular branch of the trigeminal nerve. She developed a neuropathic nerve syndrome with severe chronic pain and burning dysesthesia. She received 2 mg/kg (R)-ketamine i.m. without effect.

Patient 5. In this 69-year-old woman pain started after a minor cerebral infarction in 1981. She described her pain as constant severe aching radiating from the first premolar in the left maxilla and involving the left side of the face. Paresthesias, hyperalgesia, allodynia and symptoms indicative of sympathetic activation were present. On the first treatment she was given 0.5 mg/kg racemic ketamine i.m. On 4 subsequent occasions she received racemic ketamine or (R)-ketamine as an i.v. bolus followed by continuous infusion, the highest dose was 1 mg/kg racemate as a bolus followed by infusion of 25 mg over 30 min. She did not experience any analgesic effect.

Patient 6. In this 57-year-old woman pain started in 1980 in her right maxilla. Gradually the pain spread to involve the entire right side of the face. She described the pain as a chronic deep ache with periods of sharp pain. Paresthesia, hyperalgesia, hyperpathia and allodynia were present. She received ketamine on 4 occasions. First treatment: 1 mg/kg (R)-ketamine i.v. (no effect), second treatment: 0.5 mg/kg (S)-ketamine i.m. (pain-free 2 days), third treatment: 0.5 mg/kg racemate i.v. (no effect), 0.4 mg/kg (S)-ketamine i.v. followed by infusion of 32 mg over 30 min (no effect).

Patient 7. In this 79-year-old woman sharp pain was localized to the area innervated by the right frontal trigeminal nerve branch. She had been treated with carbamazepin for several years. In 1980 a transection of the nerve was performed, and the pain disappeared. In 1985 she reported return of the pain. This pain was chronic with burning dysesthesia, hyperalgesia and allodynia. She received 0.5 mg/kg racemic ketamine followed by infusion of 40 mg over 30 min. She was pain-free during the time period of infusion, but pain returned a few minutes after the infusion was halted.

Discussion

Both clinical and experimental studies have shown that ketamine in subanesthetic doses inhibits acute nociceptive pain in humans. The present investigation confirms that ketamine given i.m. is an effective analgesic in acute postoperative orofacial pain. The pure enantiomers (R)- and (S)-ketamine are equally effective in this type of pain, but (S)-ketamine is about 4 times more potent than (R)-ketamine. The analgesic

effect of a single i.m. dose was maximal after 5 min and lasted for less than 30 min. The plasma concentrations reached maximal levels about the same time as the analgesic effect, but the decline in analgesic effect appeared to be more rapid than the decline in plasma levels. The more rapid decline in analgesic effect may be due to a redistribution of ketamine from the brain to the blood. If this was the case, brain concentrations at the time of maximal effect might have been higher than the serum concentration measured. In experimental animals ketamine is distributed rapidly to the brain, and concentrations in brain tissue has been found to be equal to, or slightly higher than, concentrations in the blood (Gole et al. 1990). However, the possibility that the decline in analgesic effect reflects rapid tolerance development cannot be excluded.

It is well known that ketamine blocks the NMDA receptor-gated ion channel in a use-dependent way (see Lodge and Johnson 1990). It is often argued that ketamine is too unspecific and not sufficiently potent as a NMDA antagonist to serve as a probe for NMDA receptor related functions (see Reich and Silvay 1989; Lipton and Rosenberg 1994). However, both ketamine enantiomers have been found to have higher affinity for the PCP recognition site than for the other ketamine binding sites presently known (Øye et al. 1991). A K_i value of 0.6 μM for racemic ketamine in human brain was reported by Tam and Zhang (1988) who used dizocilpine as a radioactive ligand. Using TCP (a thienyl analog of PCP) as radioligand, we found slightly higher values, about 0.9 μM for (S)-ketamine and 2.5 μM for (R)-ketamine (Øye et al. 1991). At higher concentrations (S)- and (R)-ketamine interact with opioid mu-receptors (K_i values 11 and 28 μM, respectively) and *sigma* sites (K_i values 131 and 28 μM, respectively) (Øye et al. 1991). The affinities of various PCP site ligands probably depend on the prevailing subtypes of NMDA receptors, and this may account for variations in the apparent affinities found in various brain preparations. However, the clinical effects of various doses of the 2 optical isomers of ketamine occur at serum concentrations well within their respective PCP site occupancy ranges, and their relative order of clinical potency correlate positively with their PCP site affinities, but not with their affinities for *sigma* and opiate receptors which have been proposed as alternative sites of action for ketamine (Øye et al. 1991). Further, the opiate receptor antagonist, naloxone, does not inhibit the analgesic effect of ketamine in humans (Maurset et al. 1989). In the present study the maximal analgesic effects of the various forms of ketamine were obtained at serum concentrations about their respective K_i values for PCP site binding. Together these findings furnish experimental evidence for the view that the main clinical effects of ketamine in subanesthetic doses are due to inhibition of NMDA receptor-gated channels.

A number of studies have shown that NMDA receptor antagonists and NMDA channel blockers modulate nociception at the spinal level in experimental animals. A working hypothesis derived from these studies is that NMDA receptors are of particular importance in pathological (neuropathic) pain (for references see Wolf and Thompson 1991; Dubner and Ruda 1992; Dray et al. 1994). This hypothesis has attracted much attention recently and has led to the assumption that NMDA receptor antagonists or channel blockers may be used for the relief of neuropathic pain in humans. However, the clinical experience with ketamine in chronic neuropathic pain syndromes has been contradictory. Anecdotal reports that ketamine may relieve postherpetic pain has recently been confirmed in clinical trials (Klepstad et al. 1993; Eide et al. 1994). Ketamine has also been reported to be effective in patients suffering phantom limb pain (Stannard and Porter 1993) as well as in patients with other neuropathic pain syndromes (Bachonja et al. 1994).

The present results show that ketamine is not always effective as an analgesic in neuropathic pain. The prolonged analgesic effect reported by 3 patients may have been a placebo effect, but we cannot exclude the possibility of an analgesic effect due to inhibition of NMDA receptors. It is possible that analgesia due to NMDA receptor inhibition is more likely to occur in younger patients with a relatively short history of chronic pain. The time course of the analgesic effect reported by these patients differs from that reported by patients suffering acute postoperative pain and does not reflect the rapid pharmacokinetics of ketamine. A prolonged effect of ketamine has been reported previously in a patient with postherpetic neuropathic pain (Klepstad et al. 1993). The mechanism for this prolonged, analgesic effect is not clear. It is tempting to speculate that a gradual shift from NMDA receptor-dependent to NMDA receptor-independent pathways takes place during the development of neuropathic pain, and that NMDA receptors have a permissive role in this process. This might in part explain the atypical, prolonged analgesic effect and would be in line with the role played by NMDA receptors in the dorsal horn sensory neurons in rats as well as in the plasticity of other neuronal systems in particular in relation to conditioning and learning.

The mental effects of ketamine in subanesthetic doses are less severe than the psychotic 'emergence reactions' which often occur on wakening from ketamine anesthesia when benzodiazepines or other CNS depressants have not been given. Ketamine analgesia is closely associated with a general feeling of insobriety and a peculiar state of mental isolation. Blurred vision is a usual complaint. Illusions and dysperceptions are common. The clinical picture of these mental effects is in concert with the view that NMDA receptors are

involved in the cognitive processing of sensory afferent signals (Øye et al. 1991, 1992).

The mental side effects limit the use of ketamine in some patients with chronic pain. Even a slight reduction in side effects, relative to the analgesic effect, may be of clinical importance. Previous literature on ketamine clearly presents (S)-ketamine as superior to (R)-ketamine with regard to side effects. This consensus is based on the much cited article of White et al. (1980) who studied the *anesthetic* properties of the ketamine isomers. When subanesthetic doses are examined, however, we have consistently observed that the side effects of (R)-ketamine, although qualitatively similar to the side effects of (S)-ketamine, are less severe and less disturbing when equianalgesic doses are compared (Øye et al. 1992). The present work confirms this observation.

The clinical usefulness of ketamine analgesia in neuropathic pain syndromes and the possibility that NMDA receptor inhibition may interfere with the development of chronic neuropathic pain, warrants further investigations.

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