

Preliminary report on the effect of ketamine in patients with central pain

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This preliminary open prospective study reports on the effect of ketamine, an N-methyl-D-aspartate (NMDA)-receptor noncompetitive antagonist, in five patients suffering from central post-stroke pain (CPSP). Patients were evaluated at rest on a visual analogue scale (VAS) graded from 0 to 10. Pain measurement was repeated at 15 and 30 mins following intravenous administration of 0.15 to 0.25 mg/kg ketamine and then every 30 mins for 6 h. Pain evoked by light touch or cold stimulation was also measured in three patients at those times. Patients were monitored for arterial pressure, heart rate, sedation and side effects during the study. Ketamine provided a significant improvement in pain at rest and in evoked pain. A 51% to 84% decrease in the VAS score for pain at rest was observed within 60 to 180 mins. Satisfactory pain relief (more than 50% decrease in the VAS score) lasted for 150 to 210 mins. Two patients had a prolonged improvement over two or three days. Arterial pressure and heart rate did not change significantly. Mild or moderate sedation was noticed in all patients for 20 to 30 mins. These results suggest that blockade of NMDA receptors may provide pain relief in patients suffering from CPSP.

Key Words: *Central pain, Central poststroke pain, Ketamine, N-methyl-D-aspartate (NMDA) antagonists, Thalamic pain*

Etude préliminaire : Effet de la kétamine chez des patients souffrant de douleurs neuropathiques d'origine centrale

RÉSUMÉ : Cette étude prospective ouverte porte sur l'effet de la kétamine, un antagoniste des récepteurs N-méthyl-D-aspartate (NMDA), non compétitif, chez cinq patients souffrant de douleurs neuropathiques centrales après accident vasculaire cérébral, ischémique ou hémorragique. La douleur est évaluée sur une échelle visuelle analogique (EVA) de 0 à 10 avant l'injection, puis 15 et 30 minutes après l'administration intraveineuse de 0,15 à 0,25 mg/kg de kétamine, puis toutes les 30 minutes pendant 6 heures. La douleur évoquée au toucher ou au froid est également évaluée chez 3 patients, avec la même séquence. La pression artérielle, la fréquence cardiaque, la sédation et les effets secondaires sont surveillés pendant la durée de l'étude. La kétamine entraîne une diminution significative de la douleur spontanée et de la douleur évoquée. Un effet antalgique maximal de 51% à 84% est observé entre 60 et 180 minutes après l'administration de kétamine. 3 patients ont un effet antalgique satisfaisant de plus de 50% pendant 150 à 210 minutes. 2 patients ont un post-effet de 2 à 3 jours. Il n'est pas observé de modification significative de la pression artérielle et de la fréquence cardiaque. Chez tous les patients une sédation légère à modérée est notée pendant 20 à 30 minutes. Ces résultats suggèrent que le blocage des récepteurs NMDA peut entraîner un effet antalgique chez les patients souffrant de douleurs neuropathiques centrales survenant après accident hémorragique ou ischémique cérébral.

Central poststroke pain (CPSP) is a chronic neuropathic pain syndrome commonly resistant to pharmacological treatments and techniques. Allodynia, dysesthesia, hyperalgesia and sensory loss are frequently noticed in patients suffering from CPSP (1-4). In peripheral neuropathic pain, allodynia and hyperalgesia are symp-

toms related to plastic changes within the nervous system, resulting in peripheral and spinal cord sensitization (5-8) that could be mediated by N-methyl-D-aspartate (NMDA) receptor stimulation (9-17). Even if most NMDA receptors are located at the spinal cord level (18-20), NMDA receptors are also involved in synaptic transmis-

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sion in several brain areas such as the hippocampus and visual cortex (21) or ventrobasal thalamus (22,23). Blocking the NMDA receptor system might therefore provide pain relief in patients suffering from central pain syndrome. Ketamine is an NMDA receptor noncompetitive antagonist used as an anesthetic agent (24,25). It also has analgesic effects, even in subanesthetic doses (26-32). Analgesic effects of ketamine have been documented in case reports from patients with peripheral neuropathic pain (33), CPSP (33), phantom limb pain (34), chronic orofacial pain (35,36) and postherpetic neuralgia (37), and nociceptive pain in control subjects (38).

In this report we describe our assessment of the analgesic effect of ketamine in five patients suffering from CPSP.

PATIENTS AND METHODS

This study was an open prospective trial of intravenous ketamine in patients with CPSP. All patients were referred to ketamine testing after informed consent. They all suffered from documented CPSP lasting several months or years following hemispheric hematoma or infarction. CPSP was associated with allodynia, hyperalgesia or both. All patients were treated unsuccessfully with tricyclic antidepressants, neuroleptics and/or antiepileptics. Three of the five patients were premedicated with 1 mg lorazepam 1.5 h before the injection of ketamine.

Ketamine (100 mg in 10 mL) was diluted in 50 mL isotonic solution and a 0.15 to 0.25 mg/kg dose was administered intravenously over 10 mins. In one patient (patient 1), a single-blind placebo test (isotonic saline intravenous injection) was performed 30 days after ketamine administration.

Patients were previously evaluated at rest on a visual analogue scale (VAS) graded from 0 to 10. Pain measurement was repeated at 15 and 30 mins following intravenous administration and then every 30 mins for 6 h. During this period patients were monitored for arterial pressure, heart rate and sedation using a five-point scale (1: patient awake, normal vigilance; 2: patient mildly drowsy; 3: patient moderately drowsy requiring verbal stimulation; 4: patient markedly drowsy, only reactive to nociceptive stimulation; 5: patient reactive). Other side effects were also recorded. Pain evoked by light touch or cold stimulation of the corresponding cutaneous field was measured by VAS in three cases. VAS scores were analyzed using Wilcoxon test and are presented as medians and percentiles. $P < 0.05$ was considered significant.

CASE PRESENTATIONS

Patient 1

Patient 1 was a 66-year-old man who suffered from a right thalamic hematoma, documented on computed tomography (CT) scan, resulting in transient left hemiparesis. Six months later he complained of a burning pain sensation in the left arm and leg, and in the left side of the face. Pain in the left foot increased in the standing position. Pain increased in severity over four years; several pharmacological treatments, including carbamazepine, levodopa, intravenous lidocaine, levomepromazine, tricyclic antidepressants, amitriptyline and clomipramine, failed to achieve any substantial relief.

On examination he complained of allodynia to light touch, which was worst in the left upper and lower extremities and was not followed by a painful 'after-sensation'. Just before ketamine administration, pain was severe enough to compromise walking. At

that time his treatment comprised clomipramine, bromazepam and amitriptyline.

Patient 2

Patient 2, a 56-year-old woman, suffered from aneurysmal subarachnoid hemorrhage. She underwent emergency aneurysmal surgery but four days later developed a right hemiparesis related to a vasospasm. Magnetic resonance imaging and CT scan documented a small ischemic left thalamic lesion and an ischemic centrum ovale stroke. Two years later she developed pain in the right half of the body with a severe paroxysmal crisis, described as a sensation of compression and stiffness, mostly located in the right leg and shoulder. Pain was resistant to clomipramine and transcutaneous electrical nerve stimulation (TENS); cortical stimulation also failed to control it.

On examination she had a mild gentle sensory deficit to light touch and pinprick, but no allodynia, hyperalgesia or dysesthesia. Treatment, prior to ketamine injection, consisted of bromazepam, oxazepam, baclofen and amitriptyline.

Patient 3

Patient 3 was a 47-year-old woman. Transient aphasia and right hemiparesis occurred once in 1990 and twice in 1991 following a stroke in the middle cerebral artery area. CT scan showed left frontal and parietal infarcts. One week after the third stroke she developed a severe continuous burning pain sensation associated with paroxysms in the right hemiface, shoulder and arm, and in the lateral part of the thorax.

On examination she had allodynia to light touch with brief painful after-sensation, weakness of the right arm and sensory deficit in the right part of the chin. During a three-year period she underwent TENS and acupuncture, and received several drugs including clomipramine, amitriptyline, fluoxetine, carbamazepine, clonazepam and buprenorphine, which all failed to provide symptom relief. Before ketamine administration she had stopped administration of all the drugs for at least one year.

Patient 4

Patient 4, a 66-year-old man, had a history of arterial hypertension, duodenal peptic ulcer and prostatic adenocarcinoma. In June 1989 he suffered from right hemiparesis. CT scan revealed a left thalamic hematoma related to an intracranial cavernoma. A continuous burning sensation and dysesthesia in the right hand occurred one month later. Light touch produced unbearable paresthesiae. Pain was permanent but was worst at the beginning and end of the day. There had been no change in the intensity of pain for years despite intensive pain treatment including injection of corticosteroids in the carpal tunnel, amitriptyline, imipramine, TENS, clomipramine, oxitriptan, capsaicine ointment, intravenous lidocaine and chloroform-acetylsalicylic acid topical application. Pain was only relieved by cold or tepid water on the area. Before the ketamine test he was treated with clonazepam and zopiclone.

Patient 5

Patient 5 was a 59-year-old woman with a history of ophthalmic migraine, basilar artery insufficiency syndrome, arterial hypertension and stable angina. She suffered from a right middle cerebral artery

stroke, confirmed by CT scan, resulting in a left transient hemiplegia. Three months later she developed pain and hyperalgesia in the left half of her body. She described her pain as a hot and burning sensation located mostly in the left part of the face, and the left hand, thigh and knee. Examination revealed a left hemiparesis, hyperalgesia and hyperpathia to cold and light touch. Evoked pain was followed by a prolonged painful after-sensation. She also complained of prolonged burning pain when her hand was dipped into cold water. An ice cube placed on her left wrist resulted in an immediate severe pain sensation followed by a pronounced increase in the basic pain level, expanding to the left side of her body. Evoked pain might last more than 12 h after termination of stimulation. Moderate pain relief had been achieved with clomipramine, methysergide, clonazepam and piracetam. She proceeded with this treatment until administration of ketamine.

RESULTS

As documented in Figure 1, ketamine provided a significant decrease in VAS scores in pain at rest. In all patients the onset time of pain sedation was close to 15 mins. In patients 1 and 2, a decrease in pain scores of 69% and 71%, respectively, was observed at 60 mins. In patient 3, ketamine administration produced a 84% decrease in pain at 120 mins. Patient 4 had a 51% maximum pain relief at 180 mins. The maximum effects of intravenous ketamine were therefore observed within 60 to 180 mins and ranged between 51% and 84%. Patient 5 had no pain at rest. Pain scores at rest progressively increased to values measured before ketamine administration at 330 to 360 mins in patients 1, 2 and 3. Pain sedation was reported to last two days in patient 4.

A significant improvement was also noticed in evoked pain (Figure 2) and in postsensitization evoked phenomena. Pain evoked by cold stimulation was completely abolished within 15 mins in patient 5. This patient had no more evoked pain sensation during the following three days. The other two patients (patients 1 and 3) had satisfactory evoked pain relief (greater than 50%) for 150 to 210 mins, after which pain scores progressively increased to values comparable with those preceding drug administration (at 210 mins for patient 1 and after 360 mins for patient 3) (Figure 2). No significant effect on VAS score was observed in patient 1 after isotonic saline intravenous administration.

Arterial blood pressure and heart rate did not change significantly during the study period.

Side effects, observed from the start of the analgesic effect in all patients, lasted 20 to 30 mins. Side effects included mild or moderate sedation (ratings of 2 to 3 on the sedation scale) for all patients, and sensation of warmth, numbness, singing noises and feeling of detachment from the body, for some patients.

DISCUSSION

This open study points out a significant analgesic effect of intravenous ketamine in patients with CPSP. The five patients described here were given ketamine as a sedative in an unblinded manner, having been informed about the possible analgesic effect of the drug and the transient side effects; therefore a placebo effect cannot be ruled out. Considering that these patients had a long history of unsuccessful therapeutic attempts, it is nevertheless unlikely that a placebo effect could explain the striking decrease in VAS scores

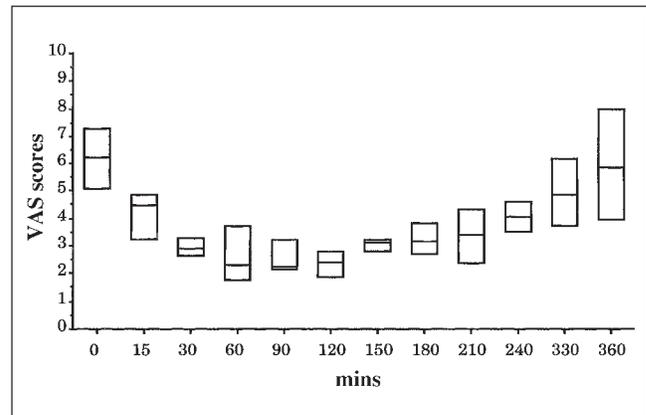


Figure 1) Pain at rest before and after intravenous administration of ketamine measured using a visual analogue scale (VAS) in four patients. Data are median; boxes represent the 25th and 75th percentiles

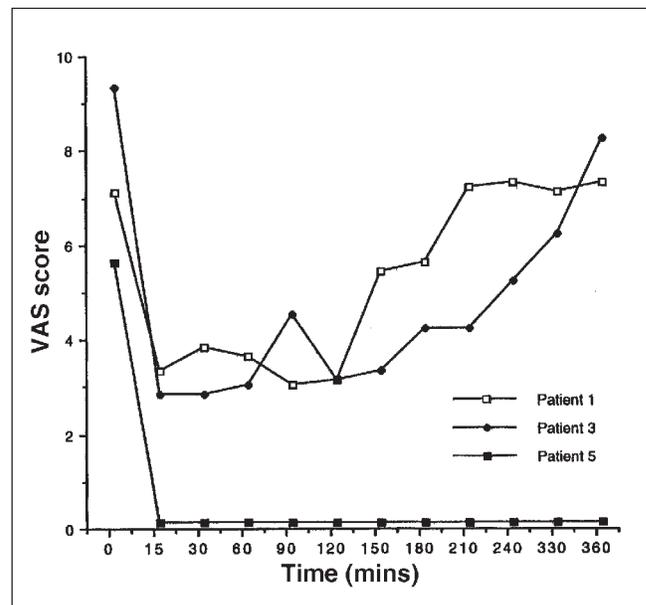


Figure 2) Individual changes in evoked pain after ketamine administration in patients 1, 3 and 5. In patient 1 pain was evoked in the foot by the standing position, in patient 3 it was evoked by gentle touch of the right arm and in patient 5 by cold stimulation on the wrist. VAS Visual analogue scale

noted in this study. Another argument supports the hypothesis of a pharmacological rather than a placebo effect: the low variability of the time course and duration of analgesia.

Backonja et al (33) reported that intravenous ketamine induced analgesia in patients with peripheral (n=3) or central pain syndrome (n=3). They described that ketamine had less effect on ongoing pain than on evoked pain and the associated after-sensation. Unlike results from the study of Backonja et al, subanesthetic doses of ketamine produced, in our five patients, an improvement in evoked pain, allodynia, hyperalgesia or dysesthesia as well as a spontaneous pain relief.

Conversely, in agreement with results from Backonja and colleagues, we report that 0.15 to 0.25 mg/kg of intravenous ketamine produced satisfactory analgesia for 2 to 3 h. After that, pain relief

persisted at a lower degree, and two patients had a prolonged incomplete analgesic effect for a few days. We also observed side effects previously described with the use of ketamine; they were transient, well tolerated and never required any treatment, but they may be a concern for CPSP chronic treatment. No relationship was documented between the ketamine dose and the decrease in VAS score, but the three different doses of ketamine were not evaluated in all patients. The series and the dose range are too limited to allow a definite conclusion on that point.

Pathogenesis and characteristics of pain are different from one patient to another; therefore response to ketamine is variable and possibly independent of minor change in dose.

Mathisen et al (36) studied the effect of ketamine in seven patients suffering from chronic orofacial pain. Ketamine had some analgesic effect in the four patients who had suffered for more than five years and had no effect in the three who had pain for less than three years. The lowest dose of ketamine used in that study was 0.4 mg/kg, higher than the doses administered in our study.

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