
CLINICAL REPORT

Oral Ketamine for the Treatment of Type I Complex Regional Pain Syndrome

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■ **Abstract:** Ketamine has been shown to be effective in the treatment of neuropathic pain. We present a case of severe complex regional pain syndrome type 1 that was treated with oral ketamine. The response and tolerability of this preparation suggest that further study is warranted. ■

Key Words: ketamine, neuropathic pain

INTRODUCTION

Complex regional pain syndrome (CRPS), as defined by the International Association for the Study of Pain (IASP) in 1994, comprises a “variety of painful conditions of regional location, secondary to injury, characterized by a distal predominance of abnormal symptoms exceeding in magnitude and duration the expected clinical course of the initial incident, and often causing important motor impairments with variable progression

over time.”¹ Such a broad concept, with a still incompletely defined pathogenesis, implies great management complexity. In this context, while many interventions have been proposed, many have proved to be ineffective. Ketamine, an N-methyl-D-aspartate (NMDA) antagonist, has been shown to be effective in the treatment of different forms of neuropathic pain. We present a case of severe pain in a patient with type I CRPS.

CASE REPORT

A 33-year-old female nurse, without previous medical history of interest, presented with left ulnar neuropathy secondary to ulnar tunnel syndrome, with the performance of a releasing epithrochleotomy in October 2000. One month later, during rehabilitation, she developed diffuse, dull pain that was described as being of a burning and electric nature, continuous during both activity and rest, and accompanied by paresthesias, allodynia, hyperpathia, and dysesthesias of the inner surface of the left forearm and elbow region, together with livedo reticularis and episodes of swelling of the fingers and forearm with vasomotor alterations (coldness) and perspiration of the entire left arm. The patient presented muscle mass loss and slight osteoporosis of the affected limb, with great functional limitation. An X-ray of the

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Submitted: June 23, 2006; Revision accepted: August 31, 2006

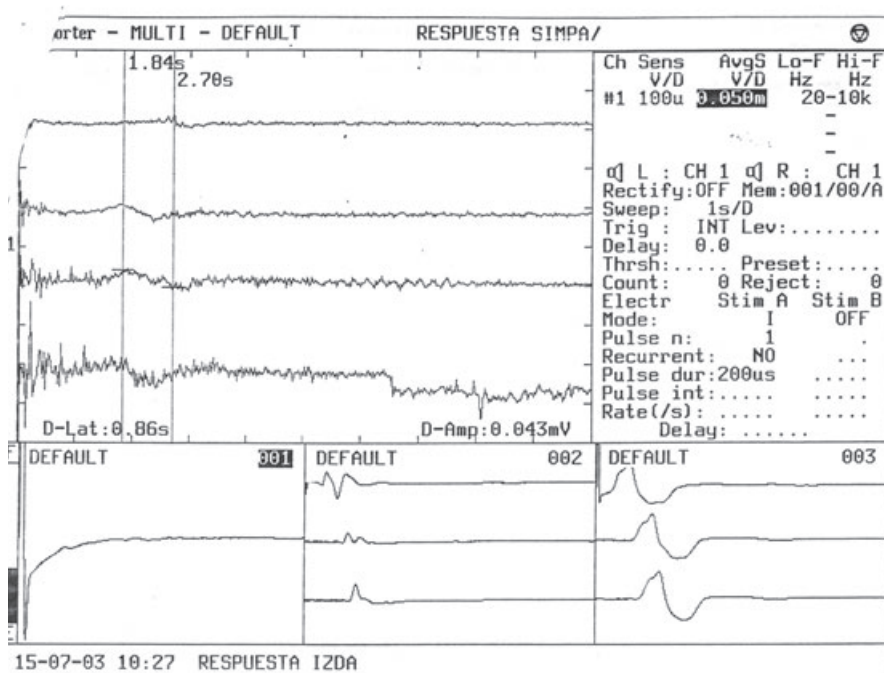


Figure 1. Electromyography (EMG): abolition of cutaneous sympathetic response in left arm, with normality of the left ulnar nerve (type I CRPS). CRPS, complex regional pain syndrome.

left forearm showed peri-articular osteopenia. Triple-phase bone scintigram revealed pathological enhanced tracer uptake in the region of the left internal ulnar condyle. Because of previous surgery performed, neurophysiological study (electromyography and electro-neurography) (Figure 1) was performed in December 2000. A diagnosis of CRPS-type I was made.

Treatment was started with nonsteroidal anti-inflammatory drugs, anticonvulsant and antidepressant medications and transcutaneous nerve stimulation alternately on/off every 2 hours. Pain control remained elusive, however. Sympathetically maintained pain was considered after positive phentolamine test and symptom control with regional brachial plexus block performed at axillary level with 20 mL of local anesthetic (0.2% ropivacaine) plus 25 µg fentanyl (Fentanest®, Valencia, Spain). Intravenous regional administration of guanethidine was carried out with a good initial response, but followed by a loss of efficacy.

After psychological evaluation (September 2002), and based on the algorithm applied on our Service,² a cervical spinal cord stimulator was implanted via the percutaneous epidural technique under sedation using radioscopy visualization. This yielded initially good symptom resolution, though the efficacy gradually decreased despite continued adequate stimulation. The clinical picture of CRPS-I reappeared 8 months after implantation.

In view of the refractoriness to the aforementioned therapies, a management protocol was designed based upon oral ketamine, in the form of ketamine syrup (10 mg/mL) prepared by hospital pharmacy, at increasing dosage. The initial visual analog scale (VAS) for pain yielded a score of 10. The previous oral treatment was maintained, i.e., topiramate 75 mg/8 hours, clonazepam 0.5 mg/8 hours, tramadol 50 mg/8 hours, amitriptyline 10 mg/24 hours, ibuprofen 600 mg/8 hours, fluoxetine 20 mg/24 hours.

The treatment protocol was started with 30 mg of oral ketamine (3 mL of syrup) every 8 hours, increasing weekly in 5 mg increments until a maximum dose of 60 mg/6 hours was reached. Significant improvement was noted, with a VAS score that decreased to 3–4 over the subsequent 4 to 5 months. The only adverse effects recorded were nausea and vomiting, which were controlled with haloperidol (0.3–0.5 mg/8 hours). However, symptoms ultimately progressed with the appearance of swelling of the face and neck, left exophthalmos and severe pain with associated color changes in the affected regions in similar fashion to the findings in the left upper extremity.

Recently (March 2005), treatment with pregabalin (75 mg/12 hours) was started. This medication was well-tolerated, except for slight dizziness, with VAS reductions from 7 to 4 in the first days. Fentanyl citrate (200 µg) was administered for breakthrough pain. Pre-

gabalin (300 mg/12 hours) had to be discontinued because of intense swelling and progressive loss of efficacy. At present, the patient continues therapy at high dosage (240 mg/day) of ketamine via the oral route, plus complementary analgesia in the form of topiramate 50 mg/12 hours, transdermal fentanyl 25 µg/72 hours, fluoxetine 20 mg/24 hours, perphenazine 2 mg/12 hours, clonazepam 1 mg/8 hours, trimethazidine 20 mg/8 hours, amitriptyline 10 mg/12 hours, and fentanyl citrate 400 µg for eruptive pain. Partial resolution (VAS 5–6) has been observed and the regime has been well-tolerated.

DISCUSSION

The definition of CRPS proposed by the IASP in 1994¹ comprises the terms “pain” as an essential element for diagnosis, and which may be either spontaneous or induced; the term “regional,” as an indication that the disproportionate and continuous pain exceeds the expected location in accordance to the apparent cause of the disorder; and finally the term “complex,” as an indication of the multiple forms of presentations of the symptoms and signs.³

Currently, it is accepted that *CRPS I* is frequently triggered by tissue injury; the term describes all patients with the above symptoms but with no underlying nerve injury. Patients with *CRPS II* experience the same symptoms but their cases are clearly associated with a nerve injury.^{4,5} The clinical manifestations of type I and II CRPS are highly variable (Table 1).

The diagnosis of type I and II CRPS is based on the anamnesis and findings through clinical exploration—though some complementary techniques may help in the differential diagnosis.^{5,6} Bone scintigram with technetium-99m is essential, and is accepted to offer objective evidence in the diagnosis of type I CRPS. In the initial phases of the bone scan, an asymmetrical increase in blood flow is characteristic, followed by enhanced tracer uptake in the affected limb.^{7,8}

The treatment of type I and II CRPS, as in other forms of chronic neuropathic pain, requires a multidisciplinary approach⁹ that may include rehabilitation, pharmacological treatment, psychological management, sympathetic block, and neurosurgical techniques. At the Dalhem conference (1998), consensus was reached on the management of CRPS—the primary objective being functional rehabilitation of the patient. In this context, adequate rehabilitation plays a crucial role, to the point that all other therapeutic measures should aim to secure increased pain control with the purpose of allowing development of the rehabilitation program.¹⁰ The success of this therapeutic algorithm focuses on functional recovery, and is based on three fundamental elements: motivation, mobilization, and desensitization.⁵

In order to reach these objectives, it is essential to achieve adequate pain control. Numerous pharmacological and nonpharmacological strategies have been proposed to this effect, and ketamine is one of the existing drug options. Many hypotheses have been proposed regarding the underlying mechanism for CRPS. Central sensitization is a key factor responsible for the development and maintenance of the neuropathic pain characteristic of the syndrome—hyperexcitability of the NMDA receptors at spinal cord and cortical layer being fundamental mediators in this phenomenon.

Ketamine is used for the induction of anesthesia, and behaves as an NMDA receptor antagonist—inhibiting glutamate-mediated activation of the latter and enhancing the effect of the inhibitory neurotransmitter GABA (gamma amine butiric acid). As a result, ketamine is presumably able to block the cell mechanisms responsible for neuronal plasticity, thereby contributing to improvement in the symptoms of patients with CRPS. Central desensitization therapy using NMDA antagonists requires: (1) patient selection, with exclusion of those in whom ketamine is contraindicated, (2) treatment individualization, performing a prior tolerability test, and (3) close patient follow-up, to assess possible side effects, and for evolutive control of the pain.

Ketamine has shown important clinical efficacy in patients with severe pain secondary to CRPS, using subanesthetic doses in both intravenous infusion¹¹ or subcutaneous infusion based on patient-controlled analgesia,¹² and in topical administration.¹³ On the other hand, the drug has also been shown to be very effective in patients with severe neuropathic pain secondary to other causes: oncological pain,¹⁴ pain of central origin secondary to stroke,¹⁵ chronic neuropathic pain of spinal origin,¹⁶ postherpetic neuralgia,¹⁷ phan-

Table 1. Clinical Manifestations of Complex Regional Pain Syndrome

- Diffuse, burning pain, in general disproportionate to the causal stimulus
- Frequent allodynia and hyperalgesia
- Early soft edematization
- Vasomotor alterations and abnormal sudomotor activity
- Limitations of joint movement
- Trophic changes: loss of bone and muscle mass in advanced phases
- Typical distal involvements. The condition may progress and even become bilateral

tom limb pain,¹⁸ restless legs syndrome,¹⁹ chronic orofacial pain,²⁰ diabetic neuropathy,²¹ and postoperative pain.²² However, we have found no reference in the literature of the clinical use of oral ketamine in patients with CRPS.

The most frequent adverse effects of ketamine involve the central nervous system, and include cognitive dysfunction, dizziness, visual hallucinations, nightmares, and even pseudo-psychiatric disorders¹⁵—though none of these problems was recorded in our case. Most of these neurological effects can be palliated by associating benzodiazepines,²³ though these pose a potential cardiovascular risk that advises against such treatment in these patients.

Previous studies have suggested that dosing via the oral route could be useful.^{14–22,24} This, and the fact that the same analgesic effect can be achieved with lower doses (up to 30% to 40% lower) using this same administration route—thereby contributing to a lessening of side effects as compared with the parenteral route²¹—led us to apply this management protocol to our patient.

The tolerability demonstrated in the therapeutic protocol applied in this case has encouraged further study to demonstrate the efficacy of the ketamine in a series of cases, and to establish the relations between dose—efficacy and dose—tolerability. This information may be helpful in the management of patients who are highly refractory to the available treatments at present, and reflects the need for pharmacological specific treatments to control the pathophysiological conditions related to CRPS.

CONCLUSION

The relevance of our clinical case is that ketamine syrup (10 mg/mL), prepared by the hospital pharmacy, was used at increasing doses as an alternative treatment for type I CRPS that was refractory to other conventional therapies. Adequate tolerability was demonstrated in this case based on close patient follow-up. The clinical usefulness was limited by the short duration of patient improvement.

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