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Advances in Translational Neuropathic Research: Example of Enantioselective Pharmacokinetic–Pharmacodynamic Modeling of Ketamine-induced Pain Relief in Complex Regional Pain Syndrome

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Abstract

Historically, complex regional pain syndrome (CRPS) was poorly defined, which meant that scientists and clinicians faced much uncertainty in the study, diagnosis, and treatment of the syndrome. The problem could be attributed to a nonspecific diagnostic criteria, unknown pathophysiologic causes, and limited treatment options. The two forms of CRPS still are painful, debilitating disorders whose sufferers carry heavy emotional burdens. Current research has shown that CRPS I and CRPS II are distinctive processes, and the presence or absence of a partial nerve lesion distinguishes them apart. Ketamine has been the focus of various studies involving the treatment of CRPS; however, currently, there is incomplete data from evidence-based studies. The question as to why ketamine is effective in controlling the symptoms of a subset of patients with CRPS and not others remains to be answered. A possible explanation to this phenomenon is pharmacogenetic differences that may exist in different patient populations. This review summarizes important translational work recently published on the treatment of CRPS using ketamine.

Keywords

Complex regional pain syndrome; Hydroxylated metabolites; Dehydronorketamine; NMDA receptor; (R,S) Ketamine; (R,S) Norketamine; Enantioselective; Pharmacokinetics; Pharmacodynamics; Cytochromes; Neuropathic pain

Introduction

For the past several decades, complex regional pain syndrome (CRPS) has puzzled scientists and clinicians. The disease process was characterized by a nonspecific diagnostic criteria, unknown etiologies, and limited therapeutic measures. Generally, the two forms of CRPS (CRPS I and CRPS II) are characterized as painful, debilitating disorders often related to previous traumatic injury [1, 2]. Previously, CRPS I and CRPS II were thought to be a variation of the same syndrome, but we now know that they are different entities. While the symptoms and progression of both CRPS I and CRPS II can be identical, it is their etiology that distinguishes them. Several therapies have been attempted with variable success. Recent studies have suggested that ketamine may be useful to treat this disease. Although there has been much interest in the use of ketamine for the treatment of CRPS, this therapy is based on clinical approaches with limited data from evidence-based studies. Currently, there is no scientific understanding of the pathological mechanisms explaining success or failure of the ketamine treatment. Clinical experience and data mostly from observational studies show variable results, with both impressive and poor response in this patient population.

Because of the vast nature and complexity of neuropathic pain, finding an appropriate animal model has been difficult [3]. Nonetheless, within the past 30 years, a variety of

experimental models for neuropathic pain have been developed [4– 7]. The availability of these different models provides an opportunity to investigate mechanisms of neuropathic pain. Finding universal features in different models will provide better insight into the most relevant mechanisms related to neuropathic pain. Through the process of reproducing a particular pain syndrome, the scientist can better understand and develop appropriate treatment options [3].

History of Ketamine

The *N*-methyl-D-aspartate (NMDA)-receptor antagonist phencyclidine was first synthesized in 1956 by Harold Maddox, PhD, at Parke-Davis (Detroit, MI) [8]. Parke-Davis pharmacologist Dr. Graham Chen, MD, PhD, subsequently showed the drug to have good anesthetic properties in animals. The compound (CI-395) underwent initial human clinical testing in 1958 by Greifenstein and colleagues [9], who, in the end, concluded that phencyclidine produced a “centrally mediated” sensory deprivation syndrome [10]. CI-395 produced unacceptably high adverse psychological effects (hallucinations and delirium) in the postanesthesia recovery period, and later was determined to be unsuitable as a human anesthetic. Dr. Calvin Lee Stevens, PhD, a professor of organic chemistry at Wayne State University and consultant for Parke-Davis, synthesized a number of phencyclidine derivatives in his laboratory. One of those, CI-581 (ketamine), first was used in a 1964 investigation by Corssen and Domino [11], who used human volunteers incarcerated at the Michigan State Prison in Jackson. Ketamine showed a favorable clinical profile, was released for clinical use in 1970, and still is frequently administered to provide anesthesia. Ketamine is a chiral compound that exists in two enantiomeric forms, (S)-ketamine and (R)-ketamine, and is primarily administered as the racemic (50:50) mixture of the two stereo-isomers. However, because (S)-ketamine is a more potent analgesic agent than the (R)-isomer [12], the single isomer has been isolated and administered (Fig. 1) [13].

Common Clinical Presentation and Diagnostic Tools in Complex Regional Pain Syndrome

Pain that occurs as a result of nerve dysfunction is categorized as neuropathic pain. The NMDA receptor serves as a mediator for active change in centrally located pain [14, 15]. An important process in central sensitization is the release of the magnesium plug on the NMDA receptor, which in turn causes an influx of calcium, leading to a host of intercellular events. The current literature demonstrates ketamine’s ability to block central sensitization by way of the drug’s compound effect on the NMDA receptor. Frequently, signs and symptoms of nociceptive and neuropathic pain may overlap. The patient’s descriptive quality of the pain is helpful in discerning if overlap of the two types of pain occurs. Often, neuropathic pain is described as a “burning” pain, while nociceptive pain is percieved as a “sharp” type of pain.

Certain questions should be raised when a physician suspects the diagnosis of neuropathic pain:

- Does the patient have a preexisting condition that may contribute to, or manifest itself with, symptoms of neuropathic pain?
- Does the patient have a history of nerve injury or trauma?
- When performing a physical examination on the patient, are there signs of allodynia or hyperpathia?
- Is there a nociceptive component to the patients' pain syndrome?
- If a sympathetic nerve block was performed, did the patient report pain relief from the procedure?

Certain chronic medical problems are associated with an increased incidence in neuropathic pain. Uncontrolled insulin-dependent and non–insulin dependent diabetes mellitus, pain occurring after herpes zoster, and pain after an amputation all are examples of medical conditions that can lead to the development of neuropathic pain.

Neuropathic pain recently has been redefined, with the addition of a projected grading system to assess the likelihood of neuropathic pain [16•]. "According to this system, the diagnosis of 'probable' neuropathic pain requires that pain have a 'distinct neuroanatomically plausible distribution,' the patient's history be 'suggestive of a relevant lesion of disease' affecting the somatosensory system, and that at least one of these be demonstrated by a confirmatory test" [16•]. For a definitive diagnosis of neuropathic pain, all four criteria need to be present.

Patients with CRPS generally present with asymmetrical distal extremity pain and edema. The occurrence of an obvious nerve injury as a causative factor differentiates CRPS I from CRPS II [17]. Therefore, patients who lack evidence of nerve transection still may carry the diagnosis of CRPS I.

Previously, the degree of CRPS was categorized by stages defined as acute, subacute, and chronic. With treatment, however, characterizing the level of disease as mild, moderate, and severe increases diagnostic validity. The initial phase of the syndrome is characterized by pain, edema, changes in skin temperature and color, and hyperhidrosis (Fig. 2) [18]. Characteristic physical examination findings with CRPS include allodynia (responding to a nonpainful stimulus with objective signs of pain) and hyperalgesia (displaying an extreme heightened response to known painful stimuli). The accurate quantification of recovery rate for CRPS is not known, although a significant number of patients with CRPS develop chronic unrelenting pain, which leads to long-term disability and a poor quality of life. Patients report an increase in their usual pain with movement, loud noises, and strong emotions. They occasionally may have involvement of more than one extremity. At the present time, the pathophysiology of CRPS I remains unknown.

Lesions and malfunctioning of the central pain pathways account for about 10% of CRPS cases. The remaining 90% of cases have been related to peripheral trauma. Important clinical signs of CRPS include autonomic dysregulation, spontaneous pain, evoked pain, and, in severely advanced cases, trophic changes [14]. The exact incidence has not been determined, but appears to occur more frequently in females [19].

The patient's response to a diagnostic block of the sympathetic nervous system with local anesthesia will inform the clinician if the pain is or is not sympathetically maintained. If there is partial or complete pain relief with a sympathetic nerve block, the pain is more likely sympathetically maintained.

A significant percentage of patients with CRPS who do not respond to interventional procedures and medication management have disease recurrence along with spread of the CRPS from its initial location. In a study by Maleki et al. [20], all 27 of their patients with CRPS I reported significant spread of their pain from the initial site to contiguous areas. The average time interval between the onset of CRPS I symptoms and the occurrence of spread was 78 days (range: 2 days to 13 months). The CRPS symptoms generally migrated distal to proximal because the initial injury was predominantly distal. However, in the six cases where the initial site was the knee, spread occurred proximally and distally [20].

Anesthetic and Subanesthetic Dosing of Ketamine with Complex Regional Pain Syndrome

Ketamine inhibits proinflammatory cytokines, which are directly involved in the processes of peripheral and central sensitization [21]. The use of ketamine in chronic pain states has been limited by severe and poorly tolerated psychotropic side effects [22]. The incidence and severity of ketamine's side effects are dose dependent, as are its analgesic potency and duration of action [23]. "Several case reports have documented reduction of pain intensity, allodynia, and associated CRPS signs of autonomic dysregulation and motor dysfunction after the administration of subanesthetic systemic, epidural, and topical ketamine" [24, 25]. An open-label trial conducted in Germany demonstrated significant pain reduction and improved functionality after the administration of ketamine in anesthetic doses in patients with CRPS symptoms [22]. A recent study by Goldberg et al. [14] showed that a 5-day continuous infusion of moderate-dose (subanesthetic) ketamine significantly reduced pain levels 3 days after the start of the infusion. Follow-up evaluations revealed that "meaningful pain relief" was reported by 40% and 60% of the patients at 3 and 6 months postinfusion, respectively. This analgesic response is consistent with their previous findings using a 10-day low-dose outpatient ketamine infusion [10]. The 5-day moderate-dose ketamine therapy used in this study provided significant reduction (≥30%) in the perceived pain level in 10 of 16 patients compared to baseline day 1 pain scores, although 6 of 16 patients reported no significant pain reduction (≤15%) [26••].

It would appear that anesthetic and subanesthetic doses of ketamine, studied both inside and outside the United States, have shown promising results in the management of CRPS pain. The precise dose that provides long-term analgesia with minimal to no side effects has yet to be determined.

Preclinical Studies

There have been multiple attempts to identify an animal model able to reproduce the clinical signs of CRPS. Unfortunately, the variability between the few current models makes it difficult to draw a direct comparison between those. To overcome this problem, Kim et al.

[3] compared three previously developed animal models using the same behavioral testing methods: 1) the chronic constriction injury by the loose ligation of the sciatic nerve (CCI) model of Bennett and Xie [4]; 2) the tight ligation of the partial sciatic nerve model of Seltzer et al. [5]; and, 3) the tight ligation of spinal nerves model of Kim and Chung [6]. The timeline of the disease process and the effects of sympathectomy served as the key points of interest. The study revealed that all three rat models of neuropathic pain demonstrated behavioral signs of both evoked (mechanical and cold allodynia) and ongoing pain [3]. This suggests that a feature common to all three methods of injury is responsible for eliciting neuropathic pain behaviors.

It is believed that neuropathic pain occurs secondary to spinal sensitization caused by excessive input of “ectopic discharges” from injured sensory neurons [16•]. Studies have shown that by blocking input at different points in the pain pathway, one may decrease the sensation of pain. Dorsal rhizotomy abolished all components of neuropathic pain in an animal model [3, 27, 28]. Application of a local anesthetic (bupivacaine) to the dorsal roots of injured segments also resulted in a (reversible) reduction of all tested behavioral signs of neuropathic pain [28]. Similarly, blocking ectopic impulse generation with application of local anesthetics to the sensitized area produced immediate relief of neuropathic pain in human patients [29]. These findings suggest that signals entering the spinal cord from injured sensory neurons are responsible for the maintenance of neuropathic pain [3].

Prospective studies have linked minor distal nerve injuries to CRPS I, but retrospective studies could not establish cause-and-effect relationships. Siegal et al. [30] demonstrated that a single needle puncture through one distal nerve is sufficient to cause some rats to develop abnormalities that resemble the behavioral and neuropathological abnormalities of CRPS in humans. This technique of needlestick distal nerve injury can reproduce signs or symptoms of CRPS that may be interpreted as psychogenic (“nonbiological”), including pain behaviors disproportionate to lesion severity, spread of pain to a new distribution, and dystonic-like hind-paw postures. Atypical hind-paw posture correlated with needle diameter, suggesting an independent mechanism in contrast to mechanical hypersensitivity reported after distal nerve injury [30]. These findings demonstrate needlestick distal nerve injury as the source of CRPS I. If reproducible, they may serve as a new and useful model of CRPS. These results support the clinical observation that factors other than the total number of injured axons influence which individuals have or do not have persistent pain after a particular injury.

Enantioselective Ketamine Metabolism

Ketamine is extensively metabolized by microsomal enzymes in humans and rats, producing a variety of metabolites. The initial metabolite is norketamine, which is produced by the N-demethylation of ketamine [31, 32], which is mediated by the hepatic cytochrome P450 enzymes (CYPs) CYP3A4, CYP2B6, and CYP2C9 [31]. This transformation has been shown to be enantioselective, with the N-demethylation of (S)-ketamine proceeding faster than that of (R)-ketamine [33]. Norketamine is further transformed by ring hydroxylation into a variety of hydroxylated metabolites and also is transformed into dehydronorketamine [31, 32]. Hydroxylated metabolites of ketamine also are produced, but to a lesser extent than the corresponding hydroxylated norketamines [31]. The CYPs associated with the

hydroxylation of ketamine and norketamine have been identified as CYP2B6 and CYP2A6, but the enantioselectivity and regioselectivity of these transformations have not been definitively determined. The hydroxylated metabolites are further transformed into glucuronides.

The extensive metabolism of the drug was reflected in an early study of metabolite profile in the 24-hour cumulative urinary excretion after a single intravenous (IV) administration, in which norketamine represented 1.6% of the administered dose, dehydronorketamine 16.1% of the dose, and the remaining drug was excreted unchanged in the urine or feces or as glucuronidates of the hydroxylated metabolites [31]. In a recent study [34], the plasma and urine concentrations of (S)-ketamine, (R)-ketamine, and their respective metabolites, obtained on day 3 of a 5-day infusion of (R,S)-ketamine using a previously described protocol, were determined in a patient with CRPS (Fig. 3) [35]. The data from this study indicate that the plasma concentration of (R)-ketamine was greater than that of (S)-ketamine (16,000 ng/mL and 12,000 ng/mL, respectively), which is consistent with other studies [36, 37]. However, the results also revealed that the major circulating metabolites were the 6-hydoxylated forms of norketamine, (2S,6S;2R,6R)-hydroxynorketamine, and (2S,6R;2R,6S)-hydroxynorketamine, whose concentrations were over 100-fold greater than the combined concentration of (S)- and (R)-norketamine [35]. This data suggests that the hydroxylated metabolites may be more important clinically than previously assumed.

Enantioselective Pharmacokinetic and Pharmacodynamic Modeling of Ketamine

Central sensitization is believed to be maintained by a high volume of nociceptive traffic [38]. The consequences of central and peripheral sensitization are a decrease in the thresholds of C- and Aδ- nociceptor firing, an increase in spread of cutaneous receptor fields of central projecting neurons, a change in spinal cord and cortical pain mapping, and an augmentation of spontaneous pain [39]. The changes in the pain pathways in CRPS lead to changes in the central, autonomic, and motor systems [40], with the NMDA receptor being key to this process. As a noncompetitive NMDA antagonist, ketamine promotes the release of the magnesium block at the NMDA receptor. The subsequent influx of calcium initiates an intercellular cascade of events, which is a critical factor in initiation of central sensitization [41]. Experimental and clinical literature demonstrate that ketamine promotes the release of the magnesium block at the NMDA receptor and that this may be the source of its effectiveness in blocking central sensitization [42]. In vitro studies have determined that (S)-ketamine is a more effective NMDA-receptor inhibitor than (R)-ketamine and that norketamine is about tenfold less active than ketamine with (S)-norketamine, a more effective NMDA-receptor inhibitor than (R)-norketamine [36].

The hydrochloride salt of ketamine, which is a secondary amine, is soluble in both water and lipids. Because of its high lipid solubility, it crosses the blood–brain barrier rapidly and is rapidly redistributed. Clinically, it has been administered using the IV, intramuscular (IM), subcutaneous, epidural, oral, rectal, and transnasal routes. The bioavailability after IV administration is about 90%, whereas bioavailability after oral and rectum administrations is

16%. This indicates that there is a significant first-pass effect by the liver. Alpha elimination, due to redistribution, has half-life on the order of a few minutes. Beta elimination, due to metabolism, has a half-life of 2 to 3 h. Oral administration of (R,S)-ketamine is accompanied by extensive first-pass metabolism, and the plasma levels of (R,S)-norketamine are about three times higher than the levels produced by IV or IM administration [37]. The plasma levels of the hydroxylated norketamine and ketamine metabolites and dehydronorketamine after oral administration of (R,S) ketamine and (R,S) norketamine have not been determined.

Metabolically (R,S)-ketamine has a relatively high clearance of 19.1 mL/(kg*min). It has a large volume of distribution in the steady state (Vss: 3.1 L/kg), owing to its low plasma-protein binding. It is 27% bound to plasma proteins, which is low compared to that of thiopental, which is 85% plasma protein–bound. Because of this large Vss and relatively rapid clearance compared to thiopental, it is clinically possible to administer ketamine as an infusion at 25 to 100 μg/min. Plasma-protein binding also explains why the IV bioavailability of ketamine is less than 100%.

The enantioselective pharmacokinetics of (S)-ketamine and (R)-ketamine have been examined in multiple studies [35, 37, 43, 44]. After single IV administration of (R,S)-ketamine, as a bolus or short infusion, the clearance of (S)-ketamine has been determined to be significantly greater than (R)-ketamine [35, 43, 44]. However, a recent study by Yanagihara et al. [37] found no significant differences in clearance between (S)-ketamine and (R)-ketamine in healthy Japanese patients. The authors suggest that the observed differences between their data and previous studies were due to pharmacogenetic differences between the Japanese population used in their study and the European population used in the earlier studies. This assumption was based upon the observation that the microsomal enzyme CYP2B6 plays a key role in the N-demethylation of ketamine and that this enzyme shows large interpopulation differences, as CYP2B6 was undetectable in 70% of Japanese patients and in 15% of Caucasian patients.

The enantioselective pharmacokinetics of (S)-ketamine and (R)-ketamine in patients with CRPS receiving a continuous 5-day infusion recently have been reported. The data from this study were similar to the data from the previous studies, in which the clearance of (S)-ketamine, $CL_{(S)} = 62.8$ L h^{-1}, was significantly greater than (R)-ketamine, $CL_{(R)} = 57.4$ L h^{-1} ($P<0.01$). This study also examined the pharmacodynamic relationships between reported pain relief and the plasma concentrations of ketamine and norketamine. No significant relationship was observed, and the data suggest that the systemic exposure to ketamine and norketamine may not be responsible for all of the drug's antinociceptive properties. Indeed, as the initial data reported above indicates (see Fig. 3), hydroxynorketamines and dehydronorketamine are the primary circulating metabolites resulting from a continuous (R,S)-ketamine. The pharmacologic and antinociceptive properties of the hydroxylated and dehydroxylated metabolites of ketamine currently are under investigation.

Conclusions

The two forms of CRPS are painful, debilitating disorders that carry a deep emotional component. Ketamine has been the focus of various studies involving the treatment of CRPS. The question as to why ketamine is effective in controlling pain symptoms in a subset of patients with CRPS and not others remains unanswered. One possible explanation of this phenomenon is pharmacogenetic differences that may exist in different patient populations. The lack of good animal models has been a recurrent theme for decades now. Finding common features in different models should provide better insight into the mechanisms critical for neuropathic pain, and identification of the uniqueness of each model should be useful for selecting a particular model for experimental animal studies.

The recent pharmacokinetic and pharmacodynamic data obtained in patients with CRPS receiving a 5-day continuous infusion of ketamine also suggest that the current “ketamine–norketamine paradigm” (ie, the assumption that the therapeutic properties of the drug are due to ketamine and norketamine and that this activity is due to the antagonism of the NMDA receptor) may not hold. The potential clinical efficacies of other ketamine metabolites are an exciting possibility and an important area of research.

Collectively, the authors involved in writing this manuscript are in agreement that neuropathic pain is indeed a multidimensional process. The diagnosis, disease course, and treatment integrate dynamic variations in the central nervous system and conformational changes at a cellular level. In anesthetic doses, ketamine’s principle effect is through its antagonistic effect on the NMDA receptor. However, the therapeutic effects observed in patients with neuropathic pain (ie, incomplete or partial improvement) after the administration of a subanesthetic dose of ketamine are not fully explained by the drug‘s effect on the NMDA receptor. lnterpatient variability and pharmacogenetic factors play a key role in what outcome is seen clinically. Thus, the current data indicate that translational neuropathic research, as well as all translational research, is an iterative process. Optimal utilization of ketamine clinically requires additional laboratory-based research to determine which metabolites are essential and how variations in drug metabolizing enzymes affect the observed analgesic effect.

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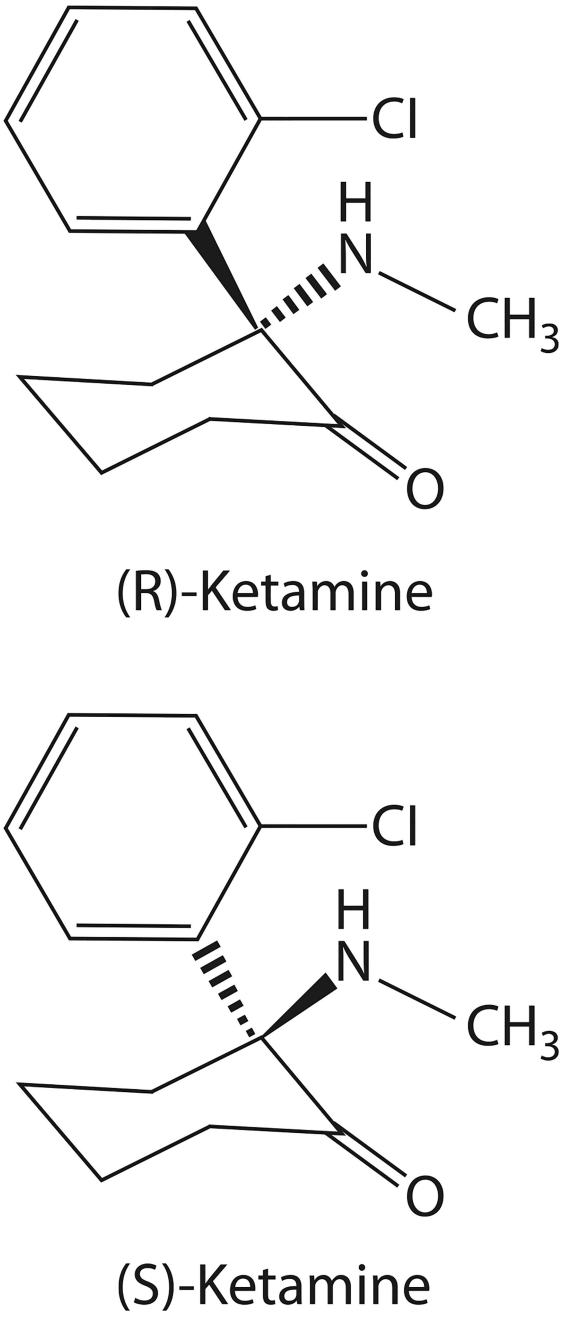

Fig. 1.
Structure of ketamine

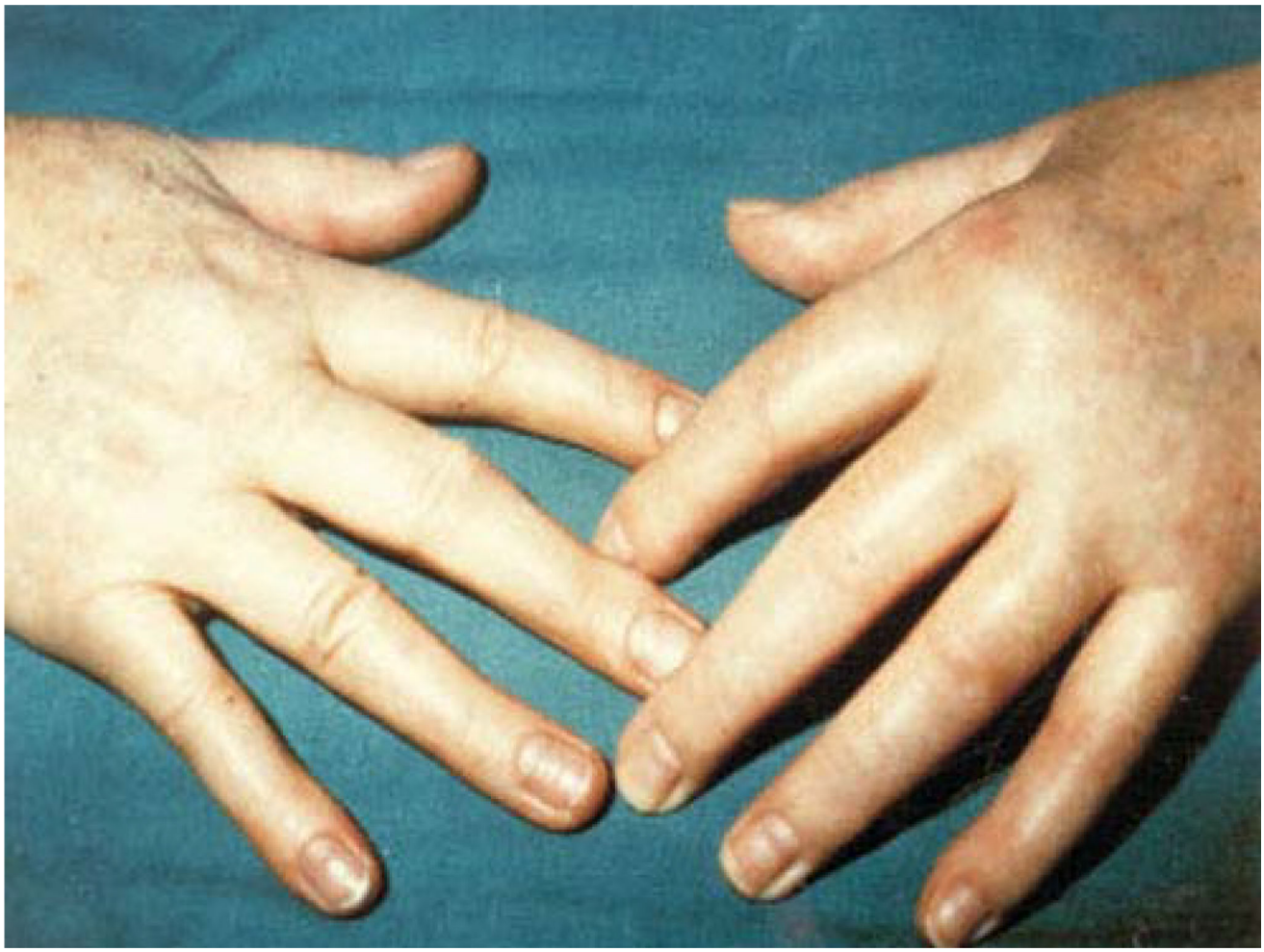

Fig. 2.

Patient with acute CRPS. The patient developed CRPS of the left hand after a radial fracture. Marked swelling appeared 2 weeks after the initial trauma. *CRPS* complex regional pain syndrome. (*From* Baron et al. [45], with permission)

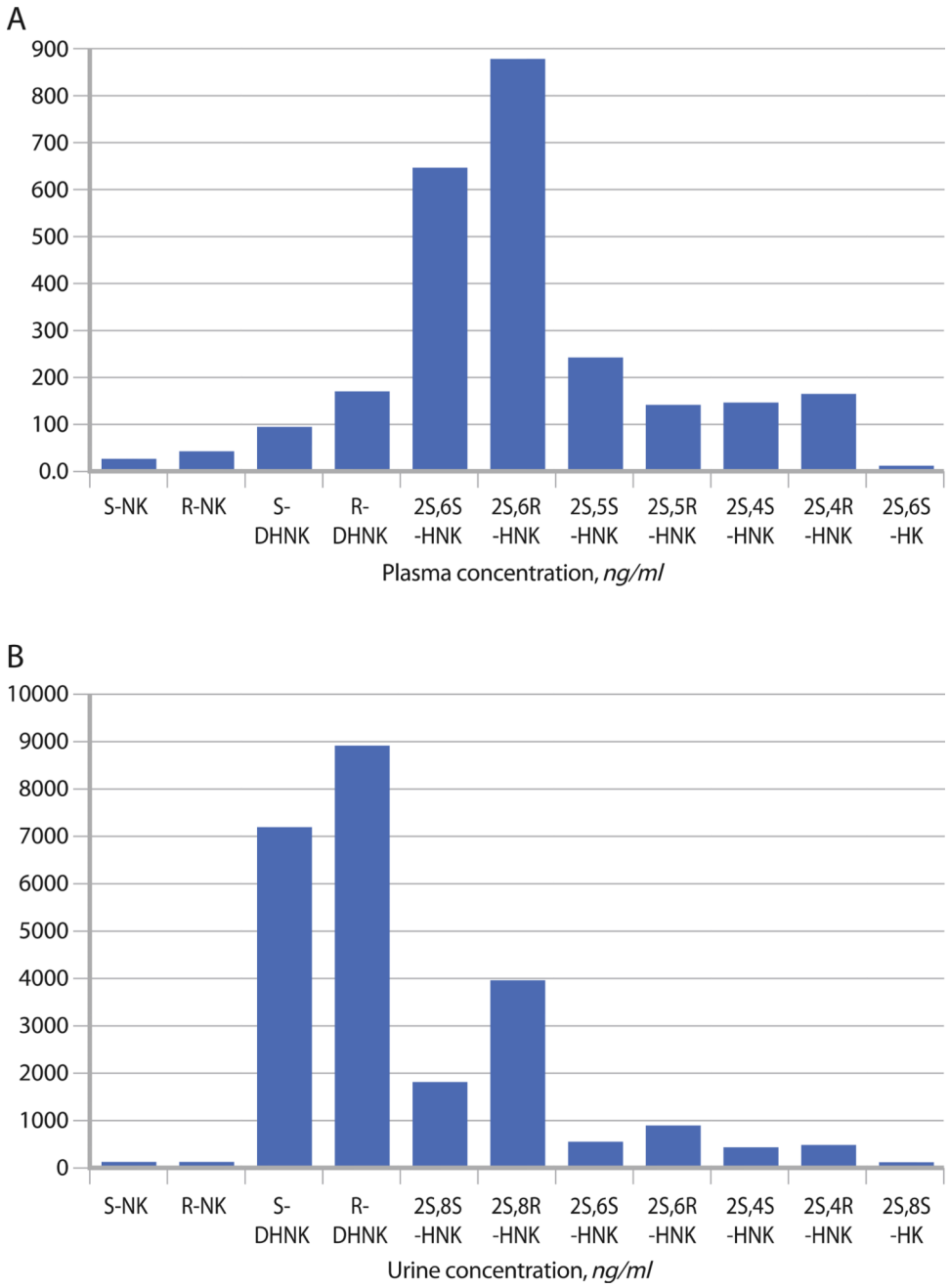

Fig. 3.

Plasma and urine concentrations of the major metabolites of (S)- and (R)-ketamine in a patient suffering from CRPS on day 3 of a 5-day continuous infusion. *CRPS* complex regional pain syndrome; *DHNK* dehydronorketamine; *HK* hydroxyketamine; *HNK* hydroxynorketamine; *NK* norketamine