The Long-Term Antinociceptive Effect of Intrathecal S(+)-Ketamine in a Patient with Established Morphine Tolerance

Sabine Sator-Katzenschlager, MD, Engelbert Deusch, MD, Petra Maier, MD, Anna Spacek, MD, and Hans G. Kress, MD, PhD

Department of Anesthesiology and Intensive Care B, University of Vienna, Vienna, Austria

Ketamine, a noncompetitive N-methyl-D-aspartate receptor antagonist, exhibits analgesic properties in rodents and humans (1–3). There are two enantiomers of ketamine, S(+)-ketamine and R(-)-ketamine. The S(+)-ketamine is the active compound. Excitatory amino acids, particularly glutamate, acting at N-methyl-D-aspartate receptors play an important role in spinal nociceptive pathways (4). Inhibition of spinal N-methyl-D-aspartate recognition sites elicits antinociception in various models of persistent pain (5,6). A series of clinical studies have suggested potent analgesia after epidural or spinal administration of racemine ketamine effects in both animals and humans (1,7–11).

We report the continuous intrathecal administration of S(+)-ketamine in a patient who suffered from insufficient pain relief despite increasing doses of intrathecal morphine and clonidine.

Case Report

A 56-yr-old (178 cm, 92 kg) obese man with a history of severe cervical and lumbar osteoarthritis and failed back surgery syndrome presented to our pain clinic for review of his intrathecal morphine therapy. In 1991 a spinal fusion was performed at the C5/C6 level, and at the L5/S1 level in 1995. Consecutive operations of the lower back followed in 1995 and 1998 because of intervertebral discus prolapse between the lumbar vertebral bodies four and five. Since 1995, in addition to the nonsteroidal antiinflammatory drug diclofenac 150 mg/d and the antidepressant amitriptyline (100 mg/d), increasing doses of oral sustained-release morphine to a maximum of 520 mg/day were required for pain relief. Because of severe side effects, an intrathecal infusion pump (Synchro Med NCY010217R9; Medtronic, Minneapolis, MN) was implanted in 1998. With an intrathecal dose of 4 mg/d morphine and 150 μg/d clonidine (Table 1) pain

relief was satisfactory, showing intensities between 3–4 on the visual analog scale (VAS; 0 = no pain, 10 = worst possible pain).

One and a half years later, the patient complained of a deep burning pain in the lumbar area, groin and both anterior thighs, and his walking distance was limited to 100 meters (VAS 8–10). The patient felt extremely uncomfortable, and the daily dose of intrathecal morphine had to be increased gradually up to 75 mg/d. In addition to the nonsteroidal antiinflammatory drug lornoxicam (16 mg/d) (we changed from diclofenac) and the antidepressant amitriptyline (75 mg/d), the anticonvulsant gabapentin (2700 mg/d) was given. By using this oral therapy, the daily dose of intrathecal morphine could gradually be reduced to 30 mg and the pain intensity decreased to approximately VAS 6. Side effects of gabapentin, however, such as edema and vertigo, led to a discontinuation of gabapentin therapy, and the pain intensity again increased to VAS 10. As morphine side effects were also present, we looked for ways to reduce the dosage of morphine and clonidine. Catheter dislocation, leakage, and malfunction of the pump were excluded.

During all the years our patient had physical therapy, as well as psychological treatments, he used transcutaneous electrical nerve stimulation. Therefore we filled the intrathecal pump with S(+)-ketamine (Ketanest® S 25 mg/mL, Parke-Davis) and morphine. After radiologic, neurologic, and psychiatric reassessment to exclude other causes of pain, we informed the patient of the possible risks of using ketamine intrathecally and got his formal informed consent. The drugs in the pump were replaced by 31.5 mg/d S(+)-ketamine and 10 mg/d morphine. This change led to a 30% pain reduction (VAS 6–7). After increasing the dose to 41.5 mg/d S(+)-ketamine and 13.3 mg/d morphine, a pain reduction of more than 50% (VAS 3–4) was achieved. The burning pain in the lumbar area, groin, and the anterior thighs remained controlled. The patient did not show any side effects or withdrawal symptoms, and he reported that he had not felt so well for more than 1 yr. He was able to walk around in the hospital without any pain or limitations. The additional pharmacological therapy included lornoxicam 16 mg/d and amitriptyline 50 mg/d.

Two weeks later, morphine could be reduced to 4.2 mg/d with 47.2 mg/d S(+)-ketamine (VAS 2–3). Blood pressure and heart rate remained stable, and he did not experience any psychotropic side effects with this intrathecal ketamine dose.

Table 1. Intrathecal Administration of Morphine Sulfate and Clonidine and Resulting Pain Intensity Expressed by the Visual Analogue Scale (VAS) (0 = No Pain; 10 = Worst Possible Pain) During the Course of the Pain History

	Start of intrathecal morphine administration	1.5 yr later			During 24-day period of intrathecal S(+)-ketamine administration			6 wk of intrathecal morphine/clonidine
					Day 4	Day 8	Day 12	
Pain score (VAS)	3–4	8–10	6	8–10	6–7	3–4	2–3	2
Intrathecal								
S(+)-ketamine (mg/d)					31.5	41.5	47.2	
Morphine-sulfate (mg/d)	4	75	30	30	10	13.3	4.2	2.2
Clonidine (µg/d)	150	150	300	300				333
Per os								
Diclofenac (mg/d)	150							
Lornixicam (mg/d)		16	16	16	16	16	16	16
Amitryptilin (mg/d)	75	75	75	75	75	50	50	50
Gabapentine (mg/d)		2700	2700					
Ranitidine (mg/d)	300							
Pantoprazol (mg/d)		20	20	20	20	20	20	20

Intrathecal S(+)-ketamine led to a marked reduction of intrathecal morphine requirement and improved pain relief. This effect persisted for 6 wk after discontinuation of intrathecal S(+)-ketamine.

Because a long-term intrathecal therapy with S(+)-ketamine had never been described in humans and because of our uncertainty about potential toxicity, we decided after 24 days (with the consent of the patient) to switch to intrathecal morphine and clonidine again (2.2 mg/d morphine and 333 µg/d clonidine). The patient continued to experience significant pain relief (VAS 2) that lasted for 6 wk. However, the pain intensity then increased to VAS 8 with burning sensations in the lower back and in both legs. Finally, the patient was successfully treated with a dual-lead spinal cord stimulation device (Synergy, Medtronic, Minneapolis, MN), which is still in place.

Discussion

In this patient who obviously became tolerant to intrathecal morphine, the additional continuous intrathecal application of S(+)-ketamine provided good analgesia and allowed the progressive reduction of the daily morphine dose without any signs of opioid withdrawal. On the basis of results from animal studies, our pain team decided to change the cosubstance to achieve a sufficient neuropathic pain therapy. Coadministration of S(+)-ketamine significantly enhanced and prolonged the antinociceptive effect of morphine in rats (12). Because it is preservative free and it is the active enantiomer, we chose S(+)-ketamine.

Until now, long-term administration of intrathecal S(+)-ketamine has not been described in patients. In our patient, the continuous intrathecal S(+)-ketamine administration was performed over a period of 24 days without any harm or undesirable effects. Six weeks after the discontinuation of intrathecal S(+)-ketamine, however, the morphine requirements increased again and a tolerance effect was noticed.

Although not very likely, the potential accumulation of intrathecal S(+)-ketamine cannot be eliminated as a possible cause for the prolonged efficacy of small-dose intrathecal morphine, even after the cessation of ketamine application.

Systemic application of the optical isomers of ketamine produced analgesia in rats (5,6,13) and humans (14). These studies used ketamine only for a short time during surgeries or bolus of ketamine in cancer patients. Walker and Cousins (14) reported the common use of intrathecal morphine with IV infusion of ketamine. A rapid reduction of the intrathecal morphine dose and hyperalgesia was facilitated by using a continuous small-dose IV infusion of ketamine. Yang et al. (7) showed in their study that coadministration of intrathecal morphine with a small dose of ketamine (2 mg) reduced the intrathecal dose of morphine required to control cancer-mediated pain and was as effective as intrathecal morphine alone. Also, Mao et al. (8) described a long-term subcutaneous infusion of ketamine that improved analgesia and reduced the morphine doses in patients with neuropathic cancer pain. Moreover, clinical studies demonstrated analgesia and reduced morphine requirements after epidural or spinal administration of racemic ketamine (1,7–11). Two reports on intrathecal administration of S(+)-ketamine in rats showed good antinociceptive activity in inflammatory pain and a synergistic antinociceptive effect with morphine (12,15).

Development of morphine tolerance is a serious problem in nonmalignant chronic pain patients, and the underlying mechanisms are not well understood (16,17). In our patient a tolerance developed even under long-term coadministration of clonidine. The results of animal studies on intrathecal coadministration of morphine and clonidine and the development

of morphine tolerance are contradictory (17,18). Fairbanks and Wilcox (17) showed that morphine and clonidine synergized in morphine tolerance. An intrathecally administered adrenergic/opioid synergistic combination might be an effective therapeutic strategy to manage pain in patients apparently tolerant to the analgesic effects of morphine. In contradiction, Plummer et al. (18) described a tolerance effect using the combination of morphine and clonidine in rats, but at a slower rate than with morphine alone.

There is little information on the potential neurotoxicity of S(+)-ketamine (19). Previous neuraxial use of ketamine raised questions about its potential toxicity (20–22). In clinical studies, neurological lesions were not reported after the short-term intrathecal use of racemic ketamine (7,9). However, preservatives such as benzethonium chloride or chlorobutanol used in racemic ketamine solutions were suspected in some cases to cause neurological damage in animals. Plain racemic ketamine did not induce spinal cord lesions but the preservative chlorobutanol did (19).

In conclusion, the combined intrathecal infusion of preservative-free S(+)-ketamine and morphine significantly improved analgesia, allowing reduction of the intrathecal morphine dosage and reversal of morphine tolerance.

The enantiomer S(+)-ketamine proved efficient in this patient who developed morphine tolerance during long-term intrathecal application and did not cause any clinically relevant side effects during continuous 24 day intrathecal infusion of as much as 47.2 mg/d.

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