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Case Report

Oral ketamine therapy in the treatment of postamputation stump pain

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Background: Hyperactivity of N-methyl-D-aspartate (NMDA) receptors may be one of the factors in the maintenance of postamputation stump pain.
Case report: Ketamine – a clinical available NMDA receptor antagonist – was administered intravenously to a patient with established stump pain in a double-blind saline-controlled fashion. Following infusion stump pain was alleviated for 31 hours. Ketamine reduced the allodynic area and wind-up-like pain and increased pressure-pain thresholds. Treatment was started with ketamine 50 mg×4 per day dissolved in juice. No side effects or development of tolerance were observed during a 3-month treatment period.
Conclusion: NMDA receptor antagonists may have a potential in the treatment of neuropathic pain, including stump pain.

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Key words: Stump pain; ketamine; NMDA receptor; mechanical stimuli; thermal stimuli.

STUMP PAIN, often associated with phantom limb pain, is a frequent complaint immediately after amputation (1). In 5–10% of cases the pain is reported to be severe, persistent and often resistant to conventional therapy (2). A large number of medical and surgical therapies have been used with limited success (3).

The mechanisms responsible for postamputation pain are not known exactly, but animal models which mimic clinical neuropathic pain have added new knowledge to the pathophysiology (4). Following nerve injury a cascade of events take place: changes in the periphery include the formation of neuromas which show an increased response to various stimuli (5). Dorsal root ganglion cells show increased spontaneous and evoked neuronal activity, and dorsal horn cells that have lost their normal afferent input become hyperexcitable. The hyperexcitability in the spinal cord includes spontaneous activity, an expansion of receptive fields and an ability of non-noxious input to evoke activity similar to that seen after C-fibre activation. There is evidence that this hyperexcitability in part is mediated by excitatory amino acids acting at NMDA receptor sites, and that excitatory amino acid receptor antagonists may block the central hyperexcitability and its clinical manifestations (6). Ketamine is an anaesthetic agent with NMDA receptor-blocking properties which reduces experimental neuropathic pain. In addition, ketamine has been reported to reduce wind-up-like pain, allodynia and spontaneous pain in clinical studies (7–13, 16).

Side effects are a major problem with the use of ketamine. We report a case in which a patient obtained excellent pain relief during oral ketamine treatment without experiencing any side effects.

Case report

A 61-year-old man presented with severe pain in both stumps following amputation at knee level bilaterally 5 months previously. Prior to surgery he suffered from severe ischaemic pain and analgesic treatment was slow-release morphine 180 mg per day. The patient never experienced phantom pain but 3 months after the amputation he developed stump pain. The pain increased in severity and at admission the pain was present constantly and interfered with his sleep. No pain relief was obtained with slow-release morphine 120 mg per day. Tricyclic antidepressants and paracetamol had been tried but were not tolerated by the patient. On examination he had well-healed stumps with no palpable neuromas.

Approval was obtained from the local Ethics Commitee and the Danish National Board of Health. Ketamine (Ketalar®, Parke-Davis) or saline was in-

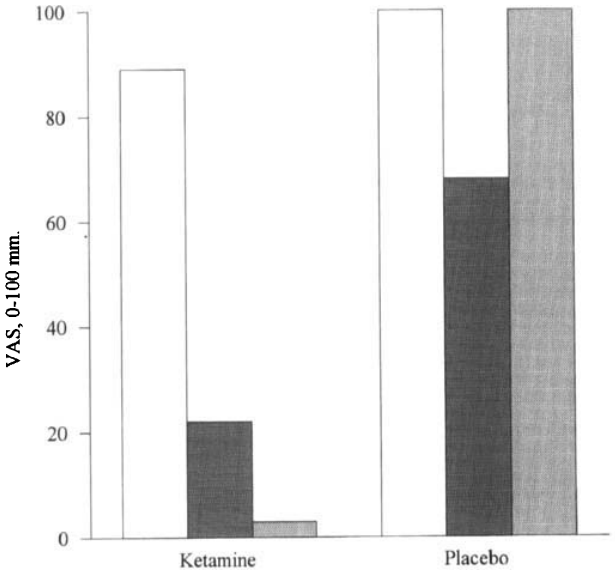

Fig. 1. The effect of ketamine and placebo on postamputation stump pain. Each bar represent the mean of 4 VAS-scores before (□), during (■) and after (▣) infusion.

fused intravenously in a double-blind fashion at two test sessions separated by 1 week. A loading dose of ketamine at 0.1 mg/kg was infused in 5 min and followed by an infusion of 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to aim at an approximately stable plasma concentration during the psychophysical measures. The infusion lasted 50 min and the patient received a total dose of ketamine of 19 mg (0.42 mg/kg).

Effect of ketamine on pain

Before and at the end of infusion the patient described his present pain by completing the Danish version of the McGill Pain Questionnaire (MPQ). Ongoing global stump pain intensity was assessed by measuring pain recording on a 100-cm visual analogue scale (VAS) (0=no pain, 100=unbearable pain) at 10-min intervals 4 times before and 4 times during infusion. After the infusion the patient recorded ongoing stump pain after 10, 20, 30 and 60 min and at home after 4, 6, 18, 24 and 48 h.

Ketamine produced a profound relief of pain. MPQ scores were reduced from 43 to 2 and from 41 to 35 for ketamine and saline, respectively. The effect of ketamine on pain intensity during and immediately after infusion is shown in Fig. 1. VAS scores were 0 at 4, 6, 18 and 24 h but pain recurred after 31 h and VAS score was 100 at 48 h.

Effect of ketamine on psychophysical measures

All measurements were carried out in the allodynic skin area on both stumps before and during infusion of ketamine/placebo.

Allodynia. Allodynia was considered present if touching with a von Frey hair at the detection threshold evoked pain. Ketamine reduced the allodynic area from 506 cm^2 to 419 cm^2 and from 125 cm^2 to 71 cm^2 for the right and left stump, respectively, whereas saline had no effect.

Wind-up-like pain. Wind-up-like pain was carried out by a modification of a procedure, previously described by Eide et al. (9). Briefly, pain was evoked by repeatedly tapping the skin at a rate of 3/s using a computer-controlled solenoid. The intensity at the peak of pain was recorded on a VAS-scale (0–100 mm). Wind-up-like pain was reduced by ketamine (by 89% and 87% for the right and left side, respectively) but increased or was unchanged by saline.

Pressure-pain thresholds (PPTs). PPTs were determined using a hand-held electronic pressure algometer. PPTs were increased on both sides following infusion of ketamine (from 184 kPa/s to 219 kPa/s and from 58 kPa/s to 292 kPa/s for the right and left stump, respectively).

Thermal sensation. Perception thresholds for cold, warmth, painful cold and heat were obtained using a Somedic Thermotest. No effect of ketamine was seen on thermal detection and pain thresholds.

Side effects

During infusion the patient was asked if he experienced specific side effects: dizziness, hallucinations, changes in hearing, reduced visual acuity etc. He reported a transient blur of vision 1–2 min after the loading dose of ketamine but no other side effects were observed.

Oral ketamine

After the double-blind session an oral dose of ketamine 50 mg, dissolved in juice because of its bitter taste, or juice without ketamine was given, blinded to the patient but unblinded to the investigator. Ketamine, but not placebo, produced in 10 min a complete relief of global stump pain which lasted for 6 h. No sensory examinations were performed following oral doses of ketamine.

The patient suffered from unbearable pain and treatment with oral ketamine was started at a daily dose of 50 mgx4. The drug was taken at meal times to minimize side effects due to rapid absorption. The patient was contacted by telephone (daily in the first 2 weeks of treatment and later weekly) and asked if he had experienced spe-

cific side effects. However, no side effects were reported during treatment. Several attempts were made to reduce the dosage of ketamine but without success, as pain always recurred. Tolerance to treatment did not seem to occur as the patient still experienced good pain relief after a 3-month treatment period.

Discussion

This case report illustrates the effectiveness of ketamine in the treatment of postamputation stump pain. Futhermore, the case shows that side effects need not be a problem with the use of ketamine.

The patient received a total dose of 0.42 mg/kg in 50 min which is below the anaesthetic effective dose. He experienced no sedation during infusion and the observed analgesic action of ketamine should be unrelated to an anaesthetic ketamine action. The prolonged analgesic effect (31 h) may represent a placebo response. However, others have found that ketamine relieved neuropathic pain for several hours and up to 3 days (11).

The allodynic area was reduced following ketamine infusion. This finding confirms the finding by others that ketamine reduces allodynia in patients suffering from neuropathic pain (12).

Experimental studies have shown that neurons in the dorsal horn exhibit the phenomenon wind-up if the stimulation is strong enough to activate C-fibres and if stimulation frequences are greater than 2–3 s^{-1}. The responses of the neurons increase with each subsequent stimulation and as a result the response to latter stimuli are greater than the initial response. Wind-up has been shown to be sensitive to NMDA receptor antagonists in experimental and clinical studies (6, 9, 10, 16). We found that ketamine reduced wind-up-like pain to repetitive mechanical stimulation of the stump.

The observation that ketamine elevates pressure-pain thresholds but does not change thermal thresholds is consistent with other studies on ketamine (9, 14, 16). It is possible that mechanical but not thermal afferent input may drive dorsal horn neurons and play a role in postamputation pain. This notion is consistent with the experimental findings that neuromas are more sensitive to mechanical than to thermal stimuli (5, 15).

In conclusion, the present case illustrates that oral ketamine may be effective in the treatment of postamputation pain. Our patient experienced no side effects and did not develop tolerance to treatment. However, an observation period of 3 months may be too short to conclude for safety from side effects and development of tolerance. Further experience is needed to asses the value of oral ketamine in long-term treatment of neuropathic pain.

References

1. Jensen TS, Rasmussen P. Phantom pain and other phenomena after amputation. In: Wall PD and Melzack R, eds. Textbook of pain. Edinburgh: Churchill Livingstone, 1994: 651–665.
2. Melsack R. Phantom limb pain: Implications for treatment of pathologic pain. *Anesthesiology* 1971: **35**: 409–419.
3. Sherman RA, Sherman CJ, Gall NG. A survey of current phantom limb treatment in the United States. *Pain* 1980: **8**: 85–99.
4. Bennett GJ. Animal models of neuropathic pain. In: Gebhart GF, Hammond DL, Jensen TS, eds. Proc. 7th World Congress on Pain. Seattle: IASP Press, 1994: 495–511.
5. Devor M, Rappaport HZ. Pain and the pathophysiology of damaged nerve. In: Wall PD, Melsack R, eds. Textbook of pain. Edingburgh: Churchill Livingstone, 1989: 47–83.
6. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993: **52**: 259–285.
7. Stannard CF, Porter GE. Ketamine hydrochloride in the treatment of phantom limb pain. *Pain* 1993: **54**: 227–230.
8. Backonja M, Arndt G, Gombar KA, Check B, Zimmermann M. Response of chronic neuropathic pain syndromes to ketamine: a preliminary study. *Pain* 1994: **56**: 51–57.
9. Eide PK, Jørum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994: **58**: 347–354.
10. Eide PK, Stubhaug A, Øye I, Breivik H. Continous subcutaneous administration of the N-methyl-D-aspartate acid (NMDA) receptor antagonist ketamine in the treatment of post-herpetic neuralgia. *Pain* 1995: **61**: 221–228.
11. Mathisen LC, Skjelbred P, Skoglund LA, Øye I. Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. *Pain* 1995: **61**: 215–220.
12. Felsby S, Nielsen J, Arendt-Nielsen L, Jensen TS. Effect of NMDA receptor antagonism with ketamine and magnesium chloride in chronic neuropathic pain. *Pain* 1995: **64**: 283–291.
13. Hoffman V, Coppejans H, Vercauteren M, Adriaensen H. Succesful treatment of postherpetic neuralgia with oral ketamine. *Clin J Pain* 1994: **10**: 240–242.
14. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesth Analg* 1995: **81**: 63–68.
15. Nyström B, Hagbarth KE. Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neuroscience Lett* 1981: **27**: 211–216.
16. Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* 1996: 67: 69–77.

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