

The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial

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Abstract

Neuropathic pain is often severe, persistent, and responds poorly to analgesic medications. Recent evidence suggests that N-methyl-d-aspartate (NMDA) receptor antagonists may be effective in the treatment of neuropathic pain. The present trial was designed to test the efficacy of acute administration of the NMDA receptor antagonist amantadine in relieving surgical neuropathic pain in patients with cancer. The study sample consisted of 15 cancer patients with the diagnosis of surgical neuropathic pain. Two 500 ml infusions of either 200 mg amantadine or placebo were administered over a 3 h period, in a randomized order, 1 week apart from each other. Spontaneous and evoked pain were measured for 48 h before treatment, during treatment, and for 48 h following treatment. An average pain reduction of 85% was recorded at the end of amantadine infusion vs. 45% following placebo administration. The difference in pain relief between the two treatments was statistically significant ($P=0.009$). Mean pain intensity remained significantly lower during the 48 h following amantadine treatment as compared with the 48 h prior to treatment (31% reduction; $P=0.006$), whereas no such effect was found with the placebo (6% reduction; $P=0.40$). Amantadine, but not the placebo, also reduced 'wind up' like pain (caused by repeated pinpricking) in four patients. We conclude that amantadine infusion is a safe and effective acute treatment for surgical neuropathic pain in cancer patients. Further trials with long-term oral or parenteral amantadine treatment should be conducted.

NMDA-Receptor Antagonists in Neuropathic Pain: Experimental Methods to Clinical Trials

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Abstract

Recent clinical data suggest that chronic pain due to nerve or soft tissue injury may result in the sensitization of the central nervous system, mediated in part by the excitatory amino acids, glutamate and aspartate. Only a handful of N-methyl-d-aspartate antagonists are clinically available. These include ketamine, dextromethorphan, memantine, and amantadine, as well as three clinically used opioids (methadone, dextropropoxyphene, and ketobemidone). This review summarizes the single-dose efficacy of the first two compounds in the treatment of experimental and neuropathic pain. In all examples presented here, NMDA-receptor antagonists with affinity at the phencyclidine site have been shown to modulate pain and hyperalgesia but are limited by dose-limiting side effects. Thus, provided their therapeutic ratio is favorable, NMDA-receptor antagonists may be effective in the treatment of some types of chronic pain.

A pilot study of the beneficial effects of amantadine in the treatment of painful diabetic peripheral neuropathy

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Abstract

Background Current symptomatic treatments for painful peripheral neuropathy in diabetes have variable efficacy in individual patients. Amongst other chemical transmitters involved in pain reception, the N-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor is involved in nociception. Amantadine was recently shown to act as a non-competitive antagonist of NMDA and may be effective in the treatment of neuropathic pain in patients with cancer. We have looked at the benefit of amantadine infusion in diabetic patients with painful peripheral neuropathy.

Methods Seventeen patients with diabetes (nine men) completed this double-blind randomized crossover placebo-controlled trial of intravenous amantadine. The average age was 58.4 (sd 11) years, with duration of diabetes of 21.1 (8.7) years and duration of painful peripheral neuropathy symptoms of 29.1 (24) months. All analgesics except paracetamol were stopped for 4 weeks prior to the study. Infusions were carried out on a weekly basis with amantadine being administered intravenously as a single 200-mg infusion. The Neuropathy Symptom Score (NSS), together with visual analogue scales, were used to assess current pain intensity (VAS-P) pre-therapy and 1 week later VAS-P was repeated together with a visual analogue scale used to assess relief in pain (VAS-R) and the Physicians Global Evaluation (PGE) score used to assess response to therapy.

Results Pre-therapy, the NSS was 6.8 (6.3–7.4) at baseline, remaining unchanged at 6.6 (5.8–7.4) after placebo ($P = 0.33$), but fell to 4.6 (3.4–5.8) after amantadine ($P = 0.003$ vs. baseline and $P = 0.02$ vs. placebo). The baseline perception of pain was scored as 7.8 cm (7.3–8.3), with no difference following placebo, at 8.2 cm (7.7–8.6) ($P = 0.34$), but following amantadine it fell to 6.2 cm (4.9–7.8) ($P = 0.01$ compared with pre-therapy, $P = 0.003$ compared with placebo). The perception of relief from pain following placebo was only 0.2 (–0.2 to +0.6) but following amantadine was 10-fold better at 1.9 (0.8–3.1) ($P = 0.016$). The PGE assessment of pain relief was –0.3 (–0.5 to 0) for placebo and following amantadine was 0.8 (0.1–1.5) ($P = 0.006$).

Conclusions Our study has shown that intravenous amantadine is beneficial in reducing the pain of painful peripheral neuropathy, with an effect sustained for at least 1 week after an infusion.