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Clinical application of amantadine, an NMDA antagonist, for neuropathic pain

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Introduction

Chronic neuropathic pain is resistant to conventional therapy, including antidepressants, anticonvulsants, and nerve blocks [1]. It has been recently suggested that neuropathic pain involves hyperactivity in the central nociceptive neurons, and that hyperactivity of *N*-methyl-D-aspartic acid (NMDA) receptors is one of the factors of this central sensitization [2–5]. NMDA receptors are considered to be involved, at least partially, in the induction and maintenance of neuropathic pain [2–5].

There are a number of studies on ketamine, one of the NMDA receptor antagonists, showing a reduction of neuropathic pain. Ketamine has been reported to reduce spontaneous pain and allodynia in patients with neuropathic pain [6–11]. Several recent studies have demonstrated the efficacy of ketamine in postherpetic neuralgia [6,7] chronic orofacial pain [8], central pain of the spinal cord [12], phantom limb [9,13], and other neuropathic pain syndromes [10]. However, the use of ketamine is limited due to its high toxicity, psychomimetic effects, and other side effects [4,7,8].

Another substance available for clinical use as an NMDA receptor antagonist is dextromethorphan, which has fewer side effects than ketamine [14,15]. However, McQuay et al. [16] showed that dextromethorphan did not have any analgesic effect in a double-blind randomized study of 19 patients compared with placebo for neuropathic pain, and Nelson et al. [17] showed that dextromethorphan has less analgesic effect in postherpetic neuralgia, diabetic neuropathy, and mixed neuropathies.

Amantadine is widely used for the management of Parkinson's disease and has recently been shown to act as a noncompetitive NMDA receptor antagonist [18,19]. Eisenberg et al. [20] showed long-term analgesic efficacy of amantadine infusion in three patients with chronic neuropathic pain. Moreover, amantadine has been reported to reduce neuropathic pain in human cancer patients in a double-blind randomized study [21]. However, the efficacy of oral amantadine in the treatment of chronic neuropathic pain has not yet been studied. The aim of this study was to investigate the efficacy of the oral administration of amantadine in relieving neuropathic pain.

Materials and methods

Nineteen patients with neuropathic pain (6 women and 13 men), 32–79 years of age, who and had been diagnosed with a variety of central and peripheral chronic neuropathic pain syndromes were enrolled in this study. All patients had been unresponsive or poorly responsive to conventional pain treatment, including antiepileptics, antidepressants, and nerve blocks (Table 1). All patients were given oral and written information about the study and the possible benefits and side effects of amantadine. Written informed consent was obtained from each participant. The study was approved by the hospital ethical committee. Treatment with oral amantadine was started at a dose of 100 mg·day^{-1} for 1 week with other medications at the time of the study, and was titrated to obtain 200 mg·day^{-1} in divided doses (twice per day). Spontaneous pain intensity was assessed by the standard 100-mm visual analogue scale (VAS) before and 4 weeks after the oral administration of amantadine.

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Table 1. Patient characteristics, responses to oral amantadine, and side effects

Subject	Sex	Age (yr)	Etiology	Pain history (mo)	Effect of oral amantadine		Side effects
					Spontaneous pain	Allodynic area	
1	M	69	PHN	3	Excellent	Complete reduction	None
2	M	60	CRPS type-1	11	No pain relief	No change	Irritation
3	M	57	Phantom pain	105	No pain relief	None	Hallucination, dry mouth
4	M	79	PHN	18	Good	Almost complete reduction	None
5	F	79	PHN	45	No pain relief	None	None
6	F	79	PHN	40	No pain relief	No change	Drowsiness, dry mouth
7	M	68	Post-thoracotomy pain	2	Excellent	Complete reduction	Laryngospasm
8	F	32	CRPS type 1	32	No pain relief	No change	Dry mouth
9	M	56	Post-thoracotomy pain	21	No pain relief	None	Involuntary movement, excitation
10	M	30	Brachial plexus avulsion	2	No pain relief	None	None
11	M	67	PHN	17	No pain relief	No change	Loss of hair
12	M	70	PHN	49	No pain relief	None	None
13	M	66	PHN	29	No pain relief	No change	None
14	F	67	PHN	6	No pain relief	No change	Drowsiness, dizziness
15	M	67	PHN	48	No pain relief	No change	Excitation, irritation, dry mouth
16	F	65	PHN	24	No pain relief	No change	None
17	M	71	PHN	2	No pain relief	None	Drowsiness
18	M	61	PHN	24	No pain relief	No change	Hallucination, dry mouth
19	M	51	Phantom pain	108	No pain relief	None	None

PHN, Postherpetic neuralgia; CRPS, complex regional pain syndrome

Furthermore, in 12 patients with allodynia, the status of mechanical allodynia from light touch was evaluated after treatment. Allodynia was determined by a cotton swab and was considered present if touching the skin evoked a clear pain sensation by standard neurological sensory examination. We evaluated allodynia before and 4 weeks after oral administration of amantadine.

The treatment response of amantadine to spontaneous pain was classified as follows. A reduction of VAS over 30% in spontaneous pain or a complete reduction of allodynia, as compared to that before drug administration, was judged to represent a case effectively treated by amantadine. Patients reporting less improvement of VAS were considered nonresponders. The Wilcoxon signed rank test was used to calculate significant differences in the mean daily pretreatment and posttreatment VAS score. Significance was accepted at $P < 0.05$.

Results

Definite pain reduction occurred in 2 of 19 patients (10.5%) after 4 weeks of oral administration of amantadine. Two patients (10.5%) had almost complete resolution of neuropathic pain and its associated allodynia. However, 17 patients (89.5%) had almost no improvement in pain control (Table 1). The mean daily pretreatment VAS score (4.49 ± 2.1) showed a slight decrease from the initial score (5.9 ± 1.2) but showed no significant change ($P = 0.05$, Wilcoxon signed rank test). Side effects were observed in 10 patients (52.6%): dry mouth in 5, drowsiness in 3, hallucination in 2, excitation in 2, irritation in 2, dizziness in 1, involuntary movement and dyskinesia in 1, and loss of hair in 1.

Discussion

In the present study, we examined whether the oral administration of amantadine relieved neuropathic pain. The oral administration of amantadine at $200\,mg \cdot day^{-1}$ significantly reduced pain and its related allodynia in two patients (10.5%). However, the majority of patients (17 of 19) (89.5%) did not experience an improvement in pain, and many patients (10 of 19) (52.6%) experienced intolerable psychic side effects.

This study was not conducted in a double-blind, placebo-controlled manner. The only two subjects with short pain duration had definite pain reduction. However, it is impossible to rule out a placebo effect in outcomes of treatments that are prescribed in an unblinded manner. Definite evidence needs to be obtained from double-blind, placebo-controlled trials.

There are several possible reasons why orally administered amantadine lacked an analgesic effect. Eisenberg and Pud [20] administered 200 mg of amantadine intravenously over a 3-h period. The peak amantadine level in the blood was believed to be much higher than the level achieved with oral administration. The high peak level of amantadine may efficiently block the so-called wind-up phenomenon [3] in neuropathic pain.

Mathinsen et al. [8] showed a gradual shift from NMDA receptor-dependent to NMDA nondependent mechanisms during the development of neuropathic pain. NMDA receptors may become less important for pain perception in neuropathic patients with a long history.

In conclusion, oral amantadine at a dosage of 200 $mg \cdot day^{-1}$ is far less promising for clinical use because of the frequent intolerable side effects and insufficient effect in reducing neuropathic pain. Further study may be required to determine the adequacy of the dose and effective means of suppressing the side effects.

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