VOLUME 103 NUMBERS 1–2 MAY 2003
PUBLISHED MONTHLY

ISSN 0304-3959
103 (1–2) 1–228

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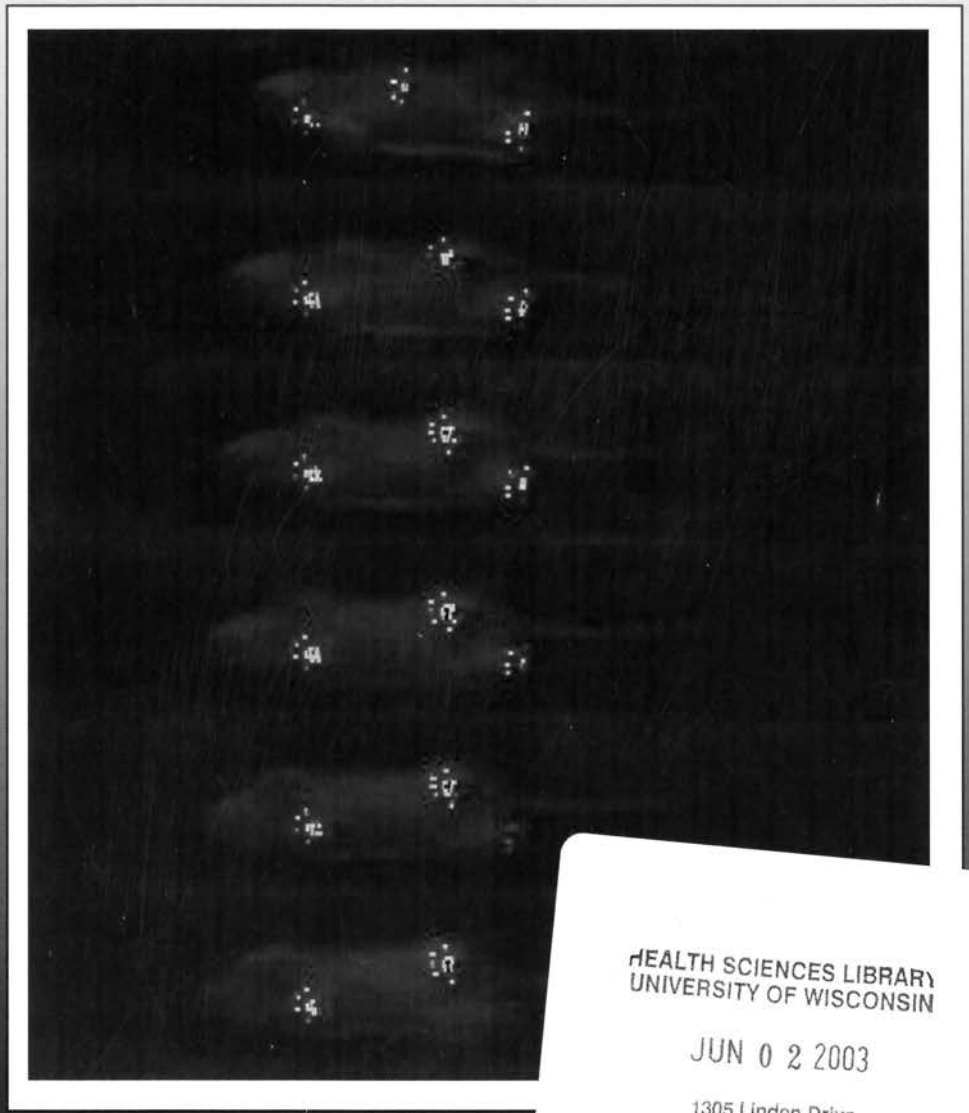

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CLINICAL NOTES

LETTERS TO THE EDITOR

Pain 103 (2003) 277–283

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Efficacy of the NMDA-receptor antagonist memantine in patients with chronic phantom limb pain – results of a randomized double-blinded, placebo-controlled trial

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Received 3 July 2002; accepted 13 November 2002

Abstract

Phantom limb pain (PLP) associated neuroplastic changes are partly mediated by excitatory amino acids at NMDA receptor sites. This study was undertaken to deduce if NMDA-receptor antagonists may be effective in patients with chronic PLP. Therefore a four week double-blinded, randomized placebo-controlled trial was performed to evaluate the efficacy of 30 mg memantine/day, an orally administrable NMDA receptor antagonist.

Thirty-six patients, 18 per group, with a history of at least 12 months PLP and an average pain of at least 4 on the 11-point numeric rating scale (NRS) were enrolled. The patients completed a standardized questionnaire before the trial. PLP intensity and the level of eight complaints were assessed during the trial. Number needed to treat (NNT) was calculated based on the average PLP during the 3rd week (steady state). In both groups, PLP declined significantly in comparison with the baseline (verum: 5.1 (±2.1) to 3,8 (±2,3), placebo from 5.1 (±2.0) to 3.2 (±1,46) NRS) without a re-rising of the PLP during the washout period. Mean pain relief was 47% in the memantine group (10 patients reported more than 50% relief), 40% in the placebo group ($6 > 50\%$): NNT were 4.5 (KI: 2.1–10.6). Analysis of covariance demonstrated a significant impact only on the prior PLP intensity, but no treatment effect. Two patients have demonstrated long-term pain relief under memantine until now (16 months). The total number of slight adverse events were comparable in both groups, but the overall number of severe events was higher in the memantine group ($P < 0.05$). This trial failed to demonstrate a significant clinical benefit of the NMDA-receptor antagonist memantine in chronic PLP. The administration of a higher dosage is probably not tolerable.

Keywords: Phantom limb pain; *N*-Methyl-D-aspartate receptor antagonist; Memantine; Placebo-controlled randomized trial

1. Introduction

Phantom limb pain (PLP) is a common complaint following upper and lower limb amputation with an incidence of 60–70% (Jensen et al., 1985; Kooijman et al., 2000). Peripheral, spinal and cerebral neuronal mechanisms may generate and maintain PLP, including plastic changes occurring in the primary somatosensory cortex (Flor et al., 1995, 1998; Birbaumer et al., 1997). Rapid cortical neuroplasticity and the hyperexcitabily in dorsal horn neurons after deafferentiation are partly mediated by excitatory amino acids at *N*-methyl-D-aspartate (NMDA) receptor sites (Garraghty and Muja, 1996; Woolf and Salter, 2000; Ji and Woolf, 2001). NMDA-receptor antagonists reduce on-going pain, allodynia and pathologically decreased pain thresholds in experimental and clinical studies in humans (Nikolajsen et al., 1996; Warncke et al., 1996; Dickenson and Sullivan, 1987; Treede et al., 1992). Ketamine is the most powerful NMDA-receptor antagonist. Using a low-dose regimen, it seems to prevent tactile hyperalgesia after surgery (Warncke et al., 1996; Stubhaug et al., 1997). Using the same ketamine dosage 72 h postoperatively, we demonstrated recently in an open pilot study a reduced intensity of PLP 6–12 months after amputation in comparison to a historical control group (Dertwinkel et al., 2002). However, the feasibility of ketamine in the treatment of chronic neuropathic pain is limited due to its psychotomimetic effects (restlessness, hallucinations, anxiety disturbances). Further-

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0304-3959/03/$30.00
doi:10.1016/S0304-3959(02)00456-6

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