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Short Communication

A placebo-controlled study of memantine for the treatment of human immunodeficiency virus–associated sensory neuropathy

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Distal sensory polyneuropathy (DSP) is the most frequent neurological complication of HIV infection. Neuropathic symptoms vary from mild paresthesias to severe pain that respond only partially to symptomatic treatment. Forty-five subjects with human immunodeficiency virus (HIV)-associated symptomatic DSP (SDSP) were enrolled in a randomized, multicenter, 16-week placebo-controlled study of memantine, an *N*-methyl-D-aspartate (NMDA) uncompetitive antagonist. Although memantine was well tolerated, no trend toward clinical benefit was observed. Results were similar to those of other pilot studies of memantine for neuropathic pain unrelated to HIV, suggesting that memantine is ineffective for the symptomatic treatment of HIV-associated SDSP. *Journal of NeuroVirology* (2006) **12,** 328–331.

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Distal sensory polyneuropathy (DSP) is the most common neurological complication of HIV infection that affects over 30% of patients even in the current era of potent antiretroviral therapy (Schifitto *et al*, 2005). The clinical presentation of symptomatic DSP (SDSP) is usually subacute and includes numbness and paresthesias in the feet that can progress to severe pain, significantly affecting activities of daily living. Signs of both large nerve fiber (decreased or absent ankle reflexes, decreased or absent vibration at the toes) and small fiber (decreased pin and temperature in a stocking distribution) pathology often coexist (Cornblath and McArthur, 1988).

The pathogenesis of human immunodeficiency virus (HIV)-associated DSP is unknown. However, as in HIV-associated cognitive impairment, products of immune activation have been implicated as an indirect mechanism of neuronal injury (Tyor *et al*, 1995). This neurotoxic effect is thought to be mediated in part by *N*-methyl-D-aspartate (NMDA) receptor activation (Jones and Power, 2006). Memantine (1-amino-3,5-dimethyladamantane), an analog of the antiviral drug amantadine, acts as an uncompetitive/fast-off-rate, low-affinity antagonist of the NMDA receptor (Chen *et al*, 1992, 1998). It has been shown that memantine can prevent the neurotoxicity induced by gp120, Tat, and platelet-activating factor (PAF), and reduce neuronal injury and loss in the gp120 transgenic mouse (Toggas *et al*,

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Giovanni Schifitto had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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1996; Lipton, 1992; Nath *et al*, 2000). In addition, NMDA activation has been proposed as a mechanism that contributes to the maintenance of chronic neuropathic pain (Sang *et al*, 2002). In this regard, memantine and other NMDA antagonists, have been shown to successfully decrease pain behavior in several rat models of chronic pain (Parsons, 2001). Therefore, there is a rationale to use NMDA antagonists to treat both HIV-associate cognitive impairment and SDSP. Based on these observations, we performed a placebo-controlled study to assess the effect of the NMDA uncompetitive antagonist memantine on HIV-associated cognitive impairment and SDSP.

The study was deigned, implemented, and analyzed by the Adult AIDS Clinical Trials Group (AACTG). All participating sites received approval by their Institutional Review Boards prior to enrolling subjects. Forest Laboratories, New Jersey, provided drug and placebo.

SDSP was defined by a neurologist based on the concomitant presence of predominantly symmetric loss or reduction of vibratory, pinprick, or temperature sensation in a stocking and glove distribution and predominantly symmetric pain or paresthesia affecting the area of abnormal sensation. The severity of pain and paresthesia was assessed by the subject on a 01–10 scale (10 = maximum pain) at baseline, weeks 4, 8, 16, and 20.

Neurologic and mood assessments were performed at baseline, weeks 4, 8, 16, and following the washout period, at week 20. Memantine dose was initiated at 10 mg per day and increased by 10 mg weekly for 4 weeks to a maintenance dose of 40 mg per day or up to the maximum tolerated dose. Memantine administration was continued to week 16 (the primary evaluation visit) followed by a 4-week drug washout period and reevaluation at week 20. HIV RNA concentration in plasma was measured by the Roche Amplicor method.

Primary analyses compared the change in pain and paresthesia indices from baseline to week 16 between the memantine and placebo arms using the Kruskal-Wallis nonparametric test. Other categorical variable comparisons were assessed by the Fisher's exact test (two-sided).

Forty-five subjects met criteria for SDSP at study entry. Twenty-four of the 45 subjects were assigned to memantine and 21 to placebo. The two groups were comparable in terms of clinical and laboratory variables (Table 1). Over 90% of the subjects were treated with potent antiretroviral therapy. A dideoxynucleoside drug (ddC, ddI, or d4T) was part of the antiretroviral regimen in 42% of the subjects in the memantine arm vs. 57% in the placebo arm (Table 1).

A majority of subjects had HIV RNA plasma concentration below the threshold of detection (Table 1). At study entry, antiretroviral therapy was unchanged for at least 6 weeks prior to study enrollment. Six subjects assigned to the placebo arm and eight patients on memantine changed their antiretroviral therapy during the study.

Twenty of the 24 subjects (83%) reached the maximum memantine dose of 40 mg during the first 16 weeks of study. At week 16, the percentage of subjects on memantine 40 mg, 30 mg, 20 mg, and 10 mg were 53%, 14%, 29%, and 5%, respectively. Three of the 21 subjects (14.20%) assigned to placebo and 4 of the 24 (16.67%) subjects assigned to memantine discontinued treatment before completion of the study.

There were no significant differences in adverse experiences between the two groups during the trial. There were no improvements in either pain (Figure 1) or paresthesia (Figure 2) measures in the memantine-treated group in comparison to the placebo group

Table 1 Demographics and clinical characteristics of subjects with SDSP at baseline

Characteristics	*Memantine* ($n = 24$)	*Placebo* ($n = 21$)	*P value*
Age, median (min, max)	44 (33, 63)	46 (31, 59)	.83*
Sex (% male)	92%	86%	.65*
Race/ethnicity† (% white)	67%	81%	.33*
Education (% ≤ high school)	4%	10%	.60*
CD4+ cells/mm^3	304 (14, 649)	268 (21, 1486)	.25*
Median (min, max)			
HIV RNA (% detectable)	81%	61%	0.29‡
Weight, kg	79.4 (50.2,148.3)	73.5 (57.0, 115.2)	.68‡
median (min, max)			
CES-D score	24.83 (10.70)	21.10 (12.09)	.17‡
Median (min, max)			
Karnofsky score (% ≤ 80)	71%	71%	.999*
Pain severity score (01–10)	6.46 (2.73)	5.80 (2.61)	.41‡
Paresthesia severity score (01–10)	4.79 (3.46)	4.30 (3.53)	.57‡
ARV therapy (% on PI)	92%	95%	.999*
Dideoxynucleoside current use	42%	57%	.376*

*Fisher's exact test (two-sided).
†Race/ethnicity data based on subject self-selection from the following categories: White; Black; Hispanic; Asian; American Indian.
‡Kruskal-Wallis test.
CES-D = Center for Epidemiological Studies—Depression Scale.

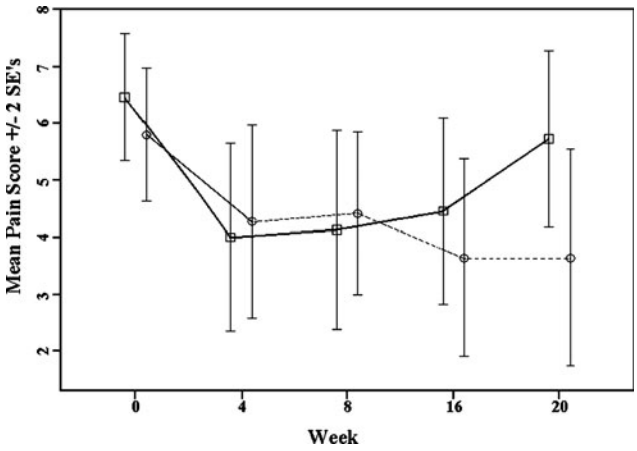

Figure 1 Mean pain severity score. Memantine (*solid line*), placebo (*dashed line*).

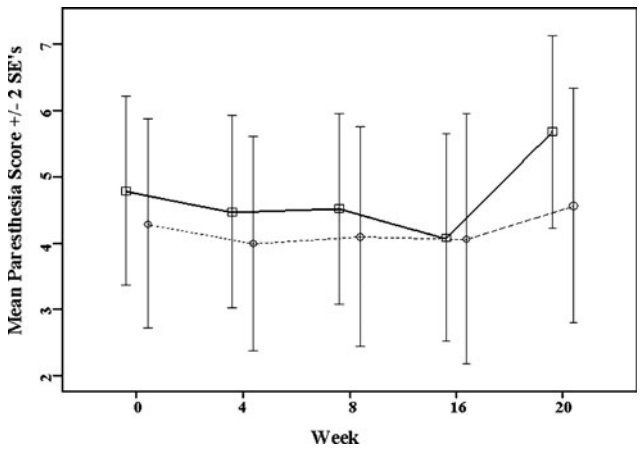

Figure 2 Mean paresthesia severity score. Memantine (*solid line*), placebo (*dashed line*).

during the 16 weeks of active treatment. The mean change in pain score from baseline to week 16 was −1.82 (standard deviation 2.77) in the memantine group and −2.36 (3.35) in the placebo group, $P = .87$. There was also no difference in the mean change of the paresthesia score between the two arms, −0.91 (3.58) memantine, −1.14 (3.35) placebo, $P = .92$. Because only 53% of the subjects were on the maximum dose (40 mg) at week 16, the data were also analyzed taking into consideration this variable. However, whether subjects were on memantine 40 mg or less than 40 mg at week 16 did not have a statistically significant impact on the mean change of pain or paresthesia score. These analyses were repeated for the subgroup of patients taking dideoxynucleoside drugs (results not shown). Changes in pain and parasthesia in this group were similar to those found in the total study group.

The results of this placebo-controlled study did not reveal benefit of memantine for the treatment of HIV-associated symptomatic distal sensory polyneuropathy (SDSP). These negative results are consistent with previous, albeit small studies in diabetic neuropathy, postherpetic neuralgia, and phantom limb pain (Sang *et al*, 2002; Maier *et al*, 2003). Recent preclinical data continue to support the role of NMDA antagonists for the treatment of neuropathic pain and several memantine derivatives are being investigated for this purpose but none so far has been shown to have any advantage over memantine (Medvedev *et al*, 2004). In contrast to DSP, memantine has been shown to improve cognitive performance in Alzheimer's disease (Reisberg *et al*, 2003; Tariot *et al*, 2004), leading to U.S. Food and Drug Administration (FDA) approval for this condition.

These results should be considered in the context of the limitations of the study design. Given the sample size, the power for the study was low for observing all but moderate to large differences between the groups. In addition, the period of observation (16 weeks) was likely too short to explore the neuroprotective effect that memantine has shown *in vitro* and in animal models of HIV neurotoxicity (Nath *et al*, 2000; Toggas *et al*, 1996; Lipton, 1992). Although our data do not favor larger studies of memantine for the treatment of HIV-associated SDSP, we cannot exclude the possibility that memantine may play a neuroprotective role in long-term studies.

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