



A Pilot Study of the Clinical Efficacy and Safety of Memantine for Huntington's Disease



Nicte I. Mejia, M.D., Christine B. Hunter, R.N., Karen Flores, and William G. Ondo, M.D.
Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas

ABSTRACT

OBJECTIVE: To determine the clinical efficacy and safety of memantine in Huntington's disease (HD). **BACKGROUND:** The excitatory activity of L-glutamate may affect the progression of HD. Memantine, an N-methyl-D-aspartate antagonist used to treat Alzheimer's dementia, could theoretically retard the progression of this disorder, improve cognition, and improve chorea. **METHODS:** HD patients were recruited from Baylor College of Medicine; twelve were started on memantine, titrated to a daily dose of 20 mg, and followed for three months. Other medications were unchanged during this period. **RESULTS:** Three patients stopped memantine because of lack of apparent efficacy (N= 1) and adverse events (N= 2). The nine analyzed patients: 5 male (55.6%), ages 53.5 years \pm 20.8, with 50.3 \pm 16.5 CAG repeats, titrated to the maximum dose of 20 mg of memantine, and were followed for 3.8 \pm 1.0 months. A significant difference existed between their initial (x= 43.2 \pm 11.7) and final (x= 33.50 \pm 11.1) total UHDRS motor scores (P= 0.008) as well as in their maximum chorea rating (4.8 \pm 3.8) (P= 0.008), compared to their initial evaluation (11.5 \pm 6.3). Patients did not show a significant change in their cognitive (P= 0.625) or behavioral (P= 0.258) ratings. Their total functional capacity (P= 0.078) and independence scale rating (P= 1.00) also failed to show a significant change [Figure 2]. Most (N= 7, 77.7%) patients did not have any adverse effects under memantine; one (11.1%) reported drowsiness; another (11.1%) complained of worsening balance, speech and social interaction. No serious adverse events were reported. **CONCLUSIONS:** In this small pilot trial, 20 mg daily dose of memantine significantly decreased chorea, but failed to improve patients cognitive, behavioral, functional, or independence ratings. Most patients tolerated memantine without side effects. Larger controlled trials and long term trials to assess for disease modification are justified.

OBJECTIVE

To determine the clinical efficacy and safety of memantine in Huntington's disease (HD).

BACKGROUND

MEMANTINE

- 1-amino-3,5-dimethyl-adamantane
- Uncompetitive NMDA-receptor modulator
- Treatment of moderate to severe dementia (e.g., Alzheimer's)
- Most common side effects include dizziness, confusion, and headache.

NMDA RECEPTOR

- Ionotropic neurotransmitter receptor
- Ligand-gated ion channel
- Several subunits
- Regional expression of NR2B receptor subunit may account for neuronal death in HD.



RATIONALE

- Overactivity of glutamate neurotoxicity may lead to neuronal death;
- HD transgenic mouse models have shown increased sensitivity to NMDA receptor activation and enhanced excitotoxicity;
- Memantine, due to its uncompetitive antagonism, prevents activation of NMDA receptors, but allows their physiologic activity, decreasing the possibility of side effects.

METHODS

We recruited HD patients from Baylor College of Medicine. Twelve patients were started on memantine. They were:

- Titrated to a daily dose of 20mg
 - Followed for 3 months
 - Other medications were unchanged during this period.
- Ascertained information included:
- Demographic data
 - Vital signs
 - UHDRS [Table 1]
 - Baseline
 - Final evaluation
 - Concomitant medications

Table 1. UHDRS.

RATING	UHRS ITEMS
Total motor	1-15
Maximum chorea	12a-12g
Cognitive	19-23
Behavioral	25a-35b
Functional	43-67
Independence	69

RESULTS

Three patients stopped memantine because of lack of apparent efficacy (N= 1) and adverse events (N= 2), patients titrated to a maximum dose of memantine and were followed for 3.8 \pm months [Table 2]. A significant difference existed between their initial (x= 43.2 \pm 11.7) and final (x= 33.50 \pm 11.1) total UHDRS motor scores (P= 0.008) as well as in their maximum chorea rating (4.8 \pm 3.8) (P= 0.008), compared to their initial evaluation (11.5 \pm 6.3) [Table 3, Figure 1]. Patients did not show a significant change in their cognitive (P= 0.625) or behavioral (P= 0.258) ratings. Their total functional capacity (P= 0.078) and independence scale rating (P= 1.00) also failed to show a significant change [Figure 2]. Most (N= 7, 77.7%) patients did not have any adverse effects under memantine; one (11.1%) reported drowsiness; another (11.1%) complained of worsening balance, speech and social interaction. No serious adverse events were reported.

Table 2. Demographic and clinical characteristics of 9 patients.

	Characteristics
Sex	5 (55.6%) male
Age (yrs)	53.5 \pm 20.8
CAG repeat length	50.3 \pm 16.5
Length of follow up	3.8 \pm 1.0 months
Adverse events	<ul style="list-style-type: none"> • Drowsiness (N = 1) • Worsening balance, speech and social interaction (N = 1)

Table 3. UHDRS Ratings before and after memantine for 9 patients.

Patient	Motor Total (Chorea)	Cognitive	Behavioral	Functional	Independence
1	41(13) / 35(3)	117 / 80	4 / 20	17 / 14	60 / 70
2	49(5) / 45(3)	R / 45	27 / 17	1 / 1	50 / 50
3	67(9) / 52(10)	C / C	9 / 19	18 / 6	50 / 50
4	31(10) / 21(5)	205 / 203	6 / N	20 / N	90 / N
5	45(17) / 24(2)	135 / 167	18 / 33	19 / 14	70 / 70
6	46(22) / 48(12)	C / R	19 / 34	39 / 1	50 / 50
7	98(17) / 73(4)	C / C	23 / 28	1 / 2	50 / 50
8	36(9) / 25(5)	64 / C	21 / 19	15 / 11	70 / 60
9	31(2) / 28(0)	163 / 141	21 / 9	15 / 18	90 / 100

Figure 1. UHDRS Motor rating before and after memantine for 9 patients.

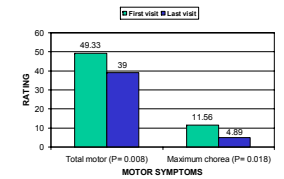
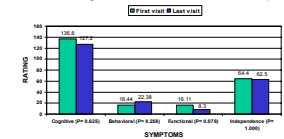


Figure 2. UHDRS ratings before and after memantine for 9 patients.



CONCLUSIONS

- In this small pilot trial, 20mg daily dose of memantine significantly decreased motor symptoms (predominantly chorea), but failed to show improvement in patient's cognitive, behavioral, functional, or independence ratings.
- Most patients tolerated memantine without side effects.
- Larger controlled trials and long term trials to assess for disease modification are justified.

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Disclosures: None.