A Randomized Trial of Amantadine in Huntington Disease

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Context: Huntington chorea, like levodopa-induced dyskinesias, may be responsive to amantadine hydrochloride treatment.

Objectives: To measure the effect of amantadine treatment on Huntington chorea and to test a hypothesis that the adventitious movements are associated with reduced central proprioception that can be corrected by amantadine treatment.

Design: A randomized placebo-controlled cross-over trial with 2 weeks of treatment.

Setting: A tertiary referral center.

Participants: Twenty-four subjects with Huntington disease took amantadine hydrochloride, 100 mg 3 times daily for 2 weeks, and placebo for 2 weeks.

Methods: Chorea of the face, trunk, and limbs while seated was videotaped at baseline and after each study phase. Segments were viewed in random order by blinded reviewers and scored. Proprioception was determined using arm restraints in which the right and left elbows were set at slightly different angles, and the errors in selecting the more extended elbow over 40 trials were recorded.

Results: The chorea score was not correlated with a proprioception deficit. Neither chorea nor proprioception were significantly affected by amantadine therapy. The chorea score was 9.6 (3.1) points at baseline and 9.7 (3.7) points when the patient was receiving amantadine therapy. The 95% confidence interval for the difference between placebo effect and amantadine effect was −1.43 to 1.0 points. Despite this, 19 subjects felt improved during the amantadine phase compared with 6 subjects improved in the placebo phase (P = .006) and the quality of life was better (P < .001).

Conclusions: Elbow proprioception was not shown to be related to Huntington chorea. Amantadine hydrochloride treatment at doses of 300 mg/d had no effect, on average, for Huntington chorea, although most patients felt subjectively better during the short course of amantadine treatment.

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CHOREA IN Huntington disease (HD) is phenomenologically similar to levodopa-induced dyskinesia in Parkinson disease. Amantadine hydrochloride therapy was found effective in reducing parkinsonian dyskinesias, raising the question of whether it might help Huntington chorea. A recent double-blind cross-over trial scoring 22 patients with HD found a median 36% reduction in extremity chorea at rest. We sought to replicate the important observation that amantadine treatment may help Huntington chorea.

Elbow proprioception was measured as a secondary outcome. We have previously shown that dopaminergic drugs acutely reduce, to a modest degree, awareness of elbow angle in Parkinson disease, despite apparently intact peripheral proprioception. A role for the basal ganglia in scaling movements based partly on proprioceptive feedback was proposed, with adventitious movements a possible result of impaired central sensitivity to limb deployment. We took the opportunity presented by the present study to test 2 hypotheses related to this model: that proprioception would be most impaired among the subjects who had HD with worst chorea and that amantadine-induced improvement in Huntington chorea would track improvement in proprioception.

Original Contribution

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results of both assays were normal in every case. Subjects gave informed consent to participate, and the study was approved by the institution’s review board. Twenty-five patients were randomized. One reported sedation and dropped out in week 1 of the first treatment phase, which was placebo in this case. Of the remaining 24, 10 were men. Mean (SD) age was 51 (13) years. Subjects had symptoms ranging in duration from 1 to 14 years (mean, 6 years). Four scored in the mildly demented range and the rest 27 or higher on the mental status examination. Three subjects were using haloperidol; and 2, quetiapine fumarate. Concomitant medications were not adjusted during the course of the study.

TREATMENTS

Subjects were randomized to take either amantadine hydrochloride, 100 mg, or placebo 3 times daily for the first 2 study weeks. At the return visit they were crossed over to the other treatment arm (Figure). Both amantadine and placebo were packaged in identical capsules. The treatment preparation and randomization order were performed by the research pharmacy, with the investigators and subjects blinded to treatments.

EVALUATION CRITERIA

The primary outcome was the change in chorea grade, specifically the average grade by the 2 of us independently viewing videotape recordings. Images were captured from videotape to a computer hard drive in individual files representing a single patient visit. Filenames from 1 to 90 were randomly designated for the baseline, middle, and final recordings of up to 30 subjects. At the end of the study all digital videotape files were sorted and viewed and scored in order of the randomized filename. Thus, graders (P.O. and R.B.D.) were thoroughly blind to whether they were viewing baseline, amantadine-treated, or placebo videotapes. Subjects had been videotaped while seated at rest for 30 seconds and while performing mental calculations (sequential subtractions) for another 30 seconds. Maximal chorea was graded absent (0), slight/intermittent (1), mild/common or moderate/intermittent (2), moderate/common (3), and marked/prolonged (4) in each of 6 body parts: face including mouth, neck-trunk, and each limb, giving a maximum score of 24 points. The face was graded during the rest period and the other body parts during the mental calculation period.

The patient’s perspective as transcribed by a nurse blinded to treatment assignment was a secondary outcome. Subjects indicated with a yes/no answer whether their condition was globally improved during the 2-week study period compared with the pretreatment baseline. Subjects also scored their chorea as marked/absent (0), slight/intermittent (1), moderate/common or moderate/intermittent (2), and marked/prolonged (4) in each of 6 body parts: face including mouth, neck-trunk, and each limb, giving a maximum score of 24 points. The face was graded during the rest period and the other body parts during the mental calculation period.

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The total number of errors of 40 trials on a previously described proprioceptive task 4 was the third outcome measure. Briefly, the subject's arms were restrained in a device and the angles of the right and left elbows adjusted. The angle at which each arm was set was in the range 86° to 94° followed a printout prepared in advance of each session. Each subject had 10 trials each with right elbow angle 2° and 4° larger and smaller than the left, the 40 trials delivered in randomized order. Both arms were put through a wide-angle extension and flexion motion between trials so that the subject could not sense the relative change in angle from 1 trial to the next. The subject was unable to see the arms owing to a blindfold and had to indicate based on proprioception which elbow felt the more extended.

RESULTS

Agreement between the observers was fair, with weighted $\kappa$ of 0.47 ($n=432$ paired scores for individual body parts). The correlation between the observers’ total chorea scores was 0.81 ($n=72$ paired scores).

Test-retest (baseline-placebo) weighted $\kappa$ was 0.48 ($n=288$ paired scores for individual body parts) and correlation coefficient for total scores was 0.80 ($n=24$ paired scores). The $\kappa$ values of 0.4 to 0.6 are typically taken to represent fair agreement.

CHOREA SEVERITY

Mean chorea score at baseline was 9.6 (3.1). At the end of the amantadine treatment period the score was 9.6 (3.7).
At the end of the placebo treatment period, the mean score was 9.3 (3.2). The 95% confidence interval for difference between amantadine and placebo was −1.43 to 1.0. The best quartile of responders scored 2.5 to 4.5 points less with amantadine compared with baseline, the worst quartile scored 2 to 7.5 points more, and the rest of the subjects changed by 2 points or less. Chorea of the face, neck, trunk, and limbs analyzed separately did not improve with amantadine treatment.

**SUBJECTIVE EFFECTS**

At the end of the amantadine treatment phase, 19 subjects reported subjective improvement in chorea compared with 6 reporting improved chorea at the end of the placebo phase (P = .006). Narrative descriptions after the amantadine treatment phase also indicated improved coordination, balance, and/or speech in more than half the subjects, with improved mental focus and energy in 2 subjects. Mean score for quality of life at the end of the amantadine treatment phase, corrected for period effect, was 3.9 (0.7). This was better than the subjective score at the end of the placebo phase 2.95 (0.7) (P < .001). Adverse effects were experienced by 10 subjects during the amantadine arm and by 4 during the placebo arm (P = .27). The adverse effects during amantadine treatment/placebo phases were insomnia (6/3), agitation or anxiety (3/1), confusion (2/1), diarrhea (2/1), sleepiness (1/0), and itch (0/1). Compliance was estimated by counting pills and questioning subjects at return visits. Two had missed doses of amantadine treatment, 2 in one case and 5 in another, while 1 subject missed 2 doses of placebo.

**PROPRIOCEPTION**

Of the 40 proprioceptive tasks, 9.4 (4.4) were inaccurately reported at baseline. At the end of the amantadine treatment phase, 8.5 (3.9) were incorrect, while at the end of the placebo phase 10.6 (5.5) were incorrect. Differences were not significant. There was no association between higher chorea scores and greater numbers of proprioceptive errors, nor between amantadine’s effects on chorea score and on proprioception.

**COMMENT**

Dopamine blockers such as haloperidol are probably the most widely used drugs to reduce Huntington chorea. Because of the risks of extrapyramidal and psychomotor adverse effects associated with these drugs, alternative treatments are desirable.

Amantadine is an old and relatively safe medication, one which neurologists are comfortable using for extended periods. It has multiple modes of action in the extrapyramidal system, among them release of dopamine from terminals, direct effects on dopamine receptors, anticholinergic action, and N-methyl-D-aspartate glutamate receptor blockade. Amantadine has been used to treat mild parkinsonism for the past 30 years, and there was a single report in 1971 of amantadine treatment helping chorea in 2 of 5 patients who had HD.6 There was, however, no clinical trial of amantadine in HD until recently, when the investigators who initially reported its effect on levodopa-induced dyskinesias performed a placebo-controlled trial in the phenomenologically similar Huntington chorea. They found a median 36% reduction in extremity chorea score with amantadine,3 with a fraction of the subjects doing even better.

We could not replicate this finding of an effect of amantadine on chorea scores. The average effect was almost 0, and for each subject who improved there was another who worsened by the same degree. Possible reasons for the differences between the studies include the statistical methods, the scoring method (while grading was the same, we treated the face as a single body part whereas face and mouth are scored separately in the standard scale used in the previous study), and the daily dose (400 mg in most patients in the previous study vs 300 mg in ours). This difference in daily dose may be important because the previous authors found outcome correlated with higher serum concentrations.

Specific limitations of our study include its short duration and passive washout period. A benefit may take longer than 2 weeks to become visible. The small cohort size lends itself to type I error, but we believe any amantadine treatment effect on chorea at rest cannot be large because no subject improved by more than 4 points and most changed by 2 points or less. The scoring system has fairly good test-retest reliability and interobserver concordance, but it may not reflect chorea outside the test setting and certainly does not capture disability and effects beyond chorea in HD.

We did find some improvements in subjective measures, raising the possibility that amantadine treatment improves some aspect of HD. Balance, coordination, and mental alertness were among the improvements reported by 19 of 24 subjects. While amantadine treatment may not have much effect on chorea, we believe a longer controlled study encompassing other aspects of HD is probably warranted based on this observation.

**REFERENCES**


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