Amantadine hydrochloride treatment in heredodegenerative ataxias: a double blind study

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Abstract

Objective—A group of 27 patients with Friedreich's ataxia and another group of 30 patients with olivopontocerebellar atrophies were each randomly divided into two subgroups, one receiving placebo and the other amantadine hydrochloride (AH; 200 mg daily) for three to four months.

Methods—The effect of double blind treatment was evaluated by simple visual and auditory reaction time (RT) and movement time (MT) for both right and left hands.

Results—The subgroup with olivopontocerebellar atrophies receiving AH showed significant improvement on seven out of eight variables studied by analysis of covariance. In patients with Friedreich's ataxia, improvement was definitely less. Treatment remained contraindicated for those with cardiomyopathies or drug intolerance.

Conclusion—The rationale of AH use in heredodegenerative ataxias can be explained by its replacement effect (dopamine release) and by direct involvement of N-methyl-D-aspartate (NMDA) in glutamate mediated neurotoxicity in cerebellar granular cells; memantine, an AH analogue, is a potent blocker of NMDA receptors.

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In preliminary investigations,[1-3] we found low concentrations of the dopamine metabolite homovanillic acid (HVA) in the CSF of patients with Friedreich's ataxia or olivopontocerebellar atrophies. Because amantadine is known to stimulate dopamine release, this finding prompted us to test amantadine hydrochloride (AH) in a few patients with Friedreich's ataxia and patients with olivopontocerebellar atrophies in open clinical trials.[1-3] In an independent, open clinical trial, Petersen et al[4] reported a beneficial effect of AH in patients with Friedreich's ataxia; treatment with AH was given on an empirical basis

The aim of the present double blind clinical trial was to verify the possible efficacy of AH (Symmetrel) treatment in Friedreich's ataxia and olivopontocerebellar atrophies, using simple reaction time (RT) and movement time

(MT) assessments exclusively as strictly objective measures.

Materials and methods

METHODS
Routine neurological examinations as well as a reinforcement technique for detecting latent parkinsonian rigidity[5] and akinesia were performed independently by two neurologists (MIB and OLP). The degree of ataxia of the upper and lower limbs was evaluated clinically as mild, moderate, or severe according to previously established criteria.[6] Ataxia in patients with olivopontocerebellar atrophies was assessed for both upper and lower limbs. In patients with Friedreich's ataxia, it was done only for the upper limbs because the patients were already paraplegic. Hand grip strength was evaluated with a Smedley dynamometer[7]; those who were unable to show a minimum grip strength of 5 kg with each hand were considered to have severe motor disturbances and were consequently ruled out from the study. The rationale for this decision was that patients with a grip strength of 5 kg are capable of pressing the RT key with a minimum force of 5 g. Every two to three weeks during the trial, the patients were telephoned to obtain information about medication compliance and possible side effects. During a visit at the end of the trial, the patients had to respond to two written questionnaires: one on possible side effects and the other about their subjective assessment of treatment. The questionnaire on side effects included insomnia, nightmares, hallucinations, depression, difficulties in concentrating, blurred vision, dizziness, loss of appetite, weight loss, and constipation. The questionnaire on the subjective assessment of treatment included general condition and mood, coordination of the upper limbs, self evaluation of dysarthria, and some specific abilities in everyday life such as the time required to cut or chop vegetables or meat for meals. In addition, patients who could walk (usually patients with olivopontocerebellar atrophy) were required to evaluate their gait and their ability to turn around, and the possibility and time required for transfer from a chair to the bath. We also evaluated the number of falls during treatment, taking as baseline the number of falls during a three month period preceding inclusion in the study. Patients were considered improved when the answers were positive for at least three variables from the above mentioned questionaire and evaluation of the number of falls.

As in our previous open study,[3] the reasons for using RT and MT as objective pretreatment and post-treatment assessments in this trial were twofold: (1) no practice effects occur in RT and MT tests[8-10]; (2) earlier work in our laboratory has shown lengthened RT and MT in patients with cerebellar disease.[11-13]

Recognised as one of the best behavioural measures of CNS integrity,[14-16] RT primarily reflects the speed and efficiency of information processing.[15] Although RT involves both central (premotor) and peripheral (muscle contraction) components, it has been shown by EMG that the central component comprises most of the stimulus-response latency and is primarily related to cognitive slowing.[17]

Whereas RT is considered to be a test of cognition, MT strictly evaluates effective motor function (motor abilities).[18] These tests are thus independent measures.[12 16 18]

Simple, forewarned visual and auditory RT and MT were studied separately with a Lafayette apparatus (model No 63107) according to the technique of Hamsher and Benton.[18] This technique allows each patient five practice trials followed by 18 trials of warned, simple visual and auditory RT and MT. After the warning signal (a white light), there is a latency period varying from two to four seconds. This period was chosen randomly, and all patients were tested in the same random order. Before the warning signal was given, the patients had to press the first of two keys with their index finger (a minimum force of 5 g was required). At the end of the latency period, a second stimulus appeared (a red light 1 cm in diameter placed centrally 1 m from the patients for the visual test or a white sound of 80 dB for the auditory test). The second stimulus was a signal for the patients to release their index finger immediately (RT), and to move it as quickly as possible to the second key (MT). The distance between the keys was 15 cm. An electronic chronometer registered RT and total time (RT + MT) in ms. To avoid methodological problems related to handedness, patients were asked to start either with the right or left hand as determined by a table of randomisation. On the final examination, they used the same sequence with their hands. The means (SEM) of RT and MT were calculated for 18 trials per patient. The following variables were determined for the right and left hands: visual RT (VRT-R, VRT-L), visual MT (VMT-R, VMT-L), auditory RT (ART-R, ART-L), and auditory MT (AMT-R, AMT-L). All measurements were conducted before and after completion of the double blind clinical trial.

Brain CT was carried out on all patients with an Elscint apparatus. Those showing central (ventricular dilatation) and cortical (cortical sulci dilatation) atrophies according to previously defined radiological criteria[19] were excluded so that only patients with clearly identified cerebellar damage were included in this study. Others excluded were alcoholic and epileptic patients and those with corrected visual acuity of less than 5/10 in one eye. Patients with cardiomyopathies and cardiac arrhythmias were also ruled out because AH is contraindicated in cardiac diseases.

PATIENTS

Patients were enrolled from the Ataxia Clinic of Hôtel-Dieu de Montréal in order of presentation at the outpatient clinic. They were also referred by the Canadian Association of Friedreich's Ataxia and recruited from the entire province of Québec. In this clinic, multidisciplinary studies are conducted.[13]

We carried out a power calculation before starting the study, taking into account our previous open clinical trial.[3] Initially, 28 patients with Friedreich's ataxia from a pool of 40 patients were included in the study. One female patient receiving active medication was taken out of the trial because of severe sleep disorders, hallucinations, and nightmares.

All patients with Friedreich's ataxia included in the trial fulfilled the diagnostic criteria of Harding.[20] Of the 27 patients who completed the clinical trial, 23 had polyneuropathies and four were diabetic. All had a bilateral cerebellar and upper motor neuron syndrome, as shown by bilateral Babinski's signs. Twelve had dorsolumbar scoliosis. Sixteen were confined to wheelchairs and the remaining 11 had a severe ataxic gait. Dysmetria and coordination disorders of the upper limbs were: moderate-severe (eight patients), moderate (10 patients), or mild (nine patients). All were right handed. Brain CT showed cerebellar atrophy in 22 patients whereas the others were normal.

Initially, 36 patients with olivopontocerebellar atrophies from a pool of 46 patients were included in this study and received AH tablets. Six of them were dropped from the study. Three of these (two women, one man) receiving placebo were not compliant with the medication. A fourth man also receiving placebo, stopped the medication because of gastrointestinal side effects. Two patients with olivopontocerebellar atrophies (one woman, one man) on active medication dropped out because of a severe sleep disorder and loss of weight respectively. Whereas the sleep disorder occurred during the first three weeks and disappeared after stopping medication, the severe weight loss in the male patient (from 100 kg to 73 kg) took place after one month of treatment.

The number of withdrawals from the subgroup of patients with olivopontocerebellar atrophies was relatively high (six out of 36) but we do not think that the exclusion of dropouts biased our results because: (1) patients dropped out before the minimum lapse of time (three months) needed for the second assessment; (2) our results concern only those patients who tolerated the medication.

Genetic studies were undertaken in Dr Guy Rouleau's laboratory.[21] Among the 30 patients with olivopontocerebellar atrophies who completed this study there were two groups with autosomal dominant olivopontocerebellar atrophies[22 23]—namely, six SCA-1 patients and 19 SCA-2 patients [21] with slow saccadic eye movements belonging to the same family from

Gaspé county. Additionally, we included three patients with recessive and two others with sporadic forms of olivopontocerebellar atrophy; in these patients, the diagnosis was made exclusively on clinical grounds. These four groups correspond to forms 3, 5, 1, and 2 of olivopontocerebellar atrophy from the clinical classification we used.[24]

Dysmetria and coordination disorders of the upper limbs were: moderate-severe (eight patients), moderate (nine patients), and mild-moderate (13 patients). Eight patients were confined to wheelchairs; the others had moderate (10 patients) and mild (12 patients) lower limb ataxias. Twelve had polyneuropathies. Four presented bilateral Babinski's signs. They did not have even mild parkinsonian signs, as evaluated by reinforcement methods.[5]

The condition of patients with Friedreich's ataxia and patients with olivopontocerebellar atrophies was stable, and they had no other medical or neurological disease. All patients with Friedreich's ataxia underwent clinical cardiological evaluation with ECGs, echocardiograms, and radioisotope ventriculography before entering the trial.

STUDY DESIGN

Both patient groups were admitted to hospital for four to five days in the metabolic ward of Hôtel-Dieu de Montréal Hospital before the trial.

Each group was randomly divided into two subgroups, one receiving two AH tablets of 100 mg each, and the other, two placebo tablets of identical size, shape, and colour as the AH tablets. Patients were included randomly in order of presentation at the outpatient clinic. Randomisation was done by KG. The neurologists (MIB and OLP) as well as the neuropsychologist (TBM) were unaware at all times of the nature of treatment given to each patient. The protocol was approved by the research ethics board of Hôtel-Dieu de Montréal Hospital, and all patients gave their informed consent.

Treatment was given to each patient for three to four months. This lapse of time was necessary because of the availability of patients who came (many of them) from Gaspé county, about 500 miles from Montreal, and also because of climatic conditions—namely, the long Canadian winter. Due to such conditions, one patient with olivopontocerebellar atrophy from Gaspé county was examined after five months (table 1). At the end of the

trial, the patients answered questionnaires about their subjective feelings and the side effects of treatment; assessments of RT and MT were performed on the same day and at the same hour as the baseline evaluation.

Both objective (RT, MT) and clinical neurological evaluations were recorded in the files before information about treatment was disclosed by the pharmacist (KG) at the end of the trial.

STATISTICS

Differences in RT and MT post-treatment values from baseline were assessed for significance within each subgroup by analysis of variance (ANOVA). The comparative effects of AH and placebo were evaluated by two way (two drug treatments by two diseases) analysis of covariance (ANCOVA) in which baseline values served as covariates for outcome values. A single common slope of regression was used whenever heterogeneity of regression was not seen at 10%. In this case, the slopes for the two categories of patients or those of the two drug treatments were used in multiple regression analysis.

Results

Table 1 gives the clinical characteristics of the patients. The patients with Friedreich's ataxia were younger than patients with olivopontocerebellar atrophies but their illness was of significantly longer duration. There was no significant difference in the duration of treatment between patients with Friedreich's ataxia and those with olivopontocerebellar atrophies ($F_{1,53} = 0.74$, NS). The mean duration of placebo treatment was mean (SEM) 3·68 (0·138) months whereas the mean duration for active treatment was 3·72 (0·187) months. The difference was not statistically significant ($F_{1,53} = 0.01$, NS).

No improvement was seen in both subgroups of patients with Friedreich's ataxia in terms of their lower limbs on both subjective assessment and neurological examination.

Subjective improvement on the self evaluation questionaire was reported by 22 patients, nine with Friedreich's ataxia and 13 with olivopontocerebellar atrophies. Except for four patients, all those who reported improvement had been treated with AH (P < 0·002).

At the end of treatment, neurological examination (blind assessment of ataxias in the upper limbs) indicated that 15 out of 29 patients were improved with AH and one of 28 was improved with placebo (P < 0·0001). Improvement with the active drug was found in patients with Friedreich's ataxia (P < 0·05) and patients with olivopontocerebellar atrophies (P < 0·001). In terms of magnitude of this effect, the ataxia scores at the level of the upper limbs were improved by 20% in patients with Friedreich's ataxia and 35% in patients with olivopontocerebellar atrophies.

In terms of side effects during treatment, which was not discontinued during the trial, two patients receiving AH had some loss of appetite during the third month. A third

Table 1   Clinical characteristics of patients

Variables	Friedreich's ataxia	Olivopontocerebellar atrophy	Significance
Sex ratio M/F	14/13	11/19	$\chi^{21} = 2.80$; NS
Age (y)	31·0 (1·4)	40 (2·0)	$F_{1,53} = 14.48$; P < 0·01
range	19–47	21–62	
Length of illness (y)	18·8 (1·45)	11·6 (1·2)	$F_{1,53} = 14.08$; P < 0·01
range	9–40	2–24	
Duration of treatment (months)	3·59 (0·19)	3·80 (0·145)	$F_{1,53} = 0.74$; NS
range	3–4	3–5*	

Except for sex ratio, all data are mean values (SEM). There was no significant difference in the characteristics of patients treated with AH and those who received placebo.
*See text: only one patient had the final evaluation after five months.

Table 2   Reaction time (RT) and movement time (MT) before and after treatment

| | Friedreich's ataxia | | | | Olivopontocerebellar atrophy | | | |
| | Placebo group n = 13 (6M, 7F) | | Amantadine group n = 14 (8M, 6F) | | Placebo group n = 15 (6M, 9F) | | Amantadine group n = 15 (5M, 10F) | |
Variables	Before	After	Before	After	Before	After	Before	After
VRT-R	476·0 (49·7)	460·0 (50·0)	472·0 (51·7)	448·0 (45·4)	416·0 (26·5)	427·0 (27·5)	453·0 (37·2)	391·0 (24·7)*
VRT-L	508·0 (67·4)	515·0 (89·7)	539·0 (66·4)	489·0 (52·4)*	430·0 (28·4)	471·0 (36·7)	425·0 (38·8)	347·0 (24·1)*
VMT-R	680·0 (110·1)	681·0 (111·4)	632·0 (92·4)	561·0 (103·8)	517·0 (62·5)	558·0 (77·9)	520·0 (59·3)	458·0 (56·0)*
VMT-L	745·0 (136·6)	825·0 (193·8)	999·0 (175·2)	651·0 (100·8)*	605·0 (80·0)	641·0 (101·0)	623·0 (88·5)	482·0 (66·7)**
ART-R	378·0 (29·7)	365·0 (31·7)	412·0 (47·8)	356·0 (30·0)*	314·0 (23·6)	334·0 (24·0)	357·0 (34·3)	311·0 (20·4)*
ART-L	405·0 (53·4)	396·0 (58·5)	480·0 (73·2)	438·0 (63·5)**	326·0 (19·7)	350·0 (24·6)	367·0 (34·5)	316·0 (19·8)*
AMT-R	588·0 (90·7)	590·0 (85·7)	696·0 (115·6)	556·0 (82·8)	483·0 (86·9)	499·0 (65·0)	479·0 (53·6)	386·0 (31·9)
AMT-L	809·0 (255·7)	782·0 (215·1)	1010·0 (218·8)	576·0 (76·5)*	477·0 (46·7)	588·0 (109·6)	552·0 (93·9)	423·0 (64·9)**

Values are means (SEM) ms.
VRT-R, VRT-L = visual reaction time with the right and left hand; ART-R, ART-L = auditory reaction time with the right and left hand; VMT-R, VMT-L, AMT-R and AMT-L = visual movement time with the right and left hand and auditory movement time with the right and left hand.
*P < 0·05; **P < 0·01, final v baseline values.

Table 3   Effect of amantadine treatment

	Friedreich's ataxia	P value	Olivopontocerebellar atrophy	P value
VRT-R	10 (58·4)	NS	64 (55·1)	< 0·05
VRT-L	31 (61·3)	NS	80 (57·8)	< 0·05
VMT-R	74 (121·4)	NS	104 (65·5)	< 0·01
VMT-L	264 (157·2)	< 0·01	236 (148·3)	< 0·01
ART-R	23 (40·6)	NS	63 (38·3)	< 0·01
ART-L	20 (44·1)	NS	84 (41·6)	< 0·01
AMT-R	97 (131·9)	NS	110 (124·4)	NS
AMT-L	200 (164)	< 0·05	427 (154·7)	< 0·01

Values are adjusted difference (±95% CI).
For abbreviations see table 2.

patient had insomnia and nightmares only during the first two weeks of AH treatment. A fourth patient receiving AH had insomnia, difficulties in concentration, and mood changes (some degree of depression) in the third month of the trial.

Whereas the clinical findings are mainly of informative value, the objective effect of AH treatment in this study was evaluated exclusively by RT and MT assessments.

Table 2 presents the RT and MT values of the four subgroups. Patients with Friedreich's ataxia and patients with olivopontocerebellar atrophies receiving AH improved in comparison with those receiving placebo.

When comparing the effects of AH with those of placebo, there were significant interactions with the disease for most variables studied. Therefore, differences between the two treatments were estimated separately for Friedreich's ataxia and olivopontocerebellar atrophies (table 3). Patients with olivopontocerebellar atrophies were significantly improved on seven RT and MT measures. Patients with Friedreich's ataxia were significantly improved on two MT measures only: visual MT with the left hand (VMT-L) and auditory MT with the left hand (AMT-L).

Among the 27 patients with Friedreich's ataxia, 19 (70·3%) asked to continue with AH treatment whereas among the 30 patients with olivopontocerebellar atrophies, 27 (90%) wanted to do so.

Discussion

We were unable to include more patients. Nevertheless, we are convinced that the improvement with AH treatment in this study is significant because the results are in agreement with those found in the previous open

clinical trial.[3] The beneficial actions of AH, considered to be related to its enhancement of dopamine release or inhibition of dopamine reuptake, were reported with some neurobehavioural and neuropsychological performances.[25-27] The percentage of side effects in our study was similar to that reported in other investigations.[28] As already reported,[28 29] the major side effects in patients who discontinued treatment as well as the minor side effects in patients who completed the study promptly disappeared with the cessation of medication.

The following points must be made regarding the rationale of AH treatment in patients with olivopontocerebellar atrophies and patients with Friedreich's ataxia Firstly, during the past few years, dopaminergic innervation of the cerebellum in mammals has been fully documented.[30 31] As stated in a previous paper,[3] we initiated AH treatment in spinocerebellar degeneration because we found low CSF HVA concentrations in our patients with olivopontocerebellar atrophies or Friedreich's ataxia, in agreement with data from other laboratories.[32] In some conditions, there is a relation between dopamine innervation of the striatum and degeneration of the olivocerebellar system.[33] Experimental dopamine depletion impairs RT.[34-36] Go and no go tasks as well as visual RT in monkeys are dependent on noradrenaline/dopamine balance.[37] Low dopamine and HVA concentrations have been recorded in the striatum of patients with end stage, dominantly inherited olivopontocerebellar atrophy.[38] Parkinsonian features are not as common as generally supposed in patients with olivopontocerebellar atrophies. Two patients from our series with mild akinesia and rigidity were excluded from this study (see methods). Therefore, none of our 30 patients with olivopontocerebellar atrophies exhibited akinesia. The findings of Kish *et al*[38] are similar to ours: none of their 14 patients with olivopontocerebellar atrophy had akinesia or ridigity.

Both tables 2 and 3 show an unforeseen result—namely, the improvement with AH was more striking with use of the left hand, which tests right hemispheric performance. To explain these handedness differences: (1) we think that there are no methodological problems because patients started RT and MT performances randomly with the right or left

hand; (2) there is right hemispheric superiority for sustained attention tasks,[39] a function which is basically involved in both RT and MT performances; (3) the mesolimbic dopamine system is implicated in incentive motivational processes by which evaluative processes are translated into action; whereas this sustained attentional system is underlaid mainly by dopaminergic mesolimbic projections,[36] selective attentional and arousal mechanisms are underpinned by noradrenergic projections[40]; moreover, the mesolimbic system is also intimately involved in the control of motor behaviour and higher integrative functions[36 41]; (4) in both humans and animals, relatively higher concentrations of dopamine are found in the left hemisphere than in the right[42] whereas the reverse is true for noradrenaline.[43]

Our hypothesis concerning this handedness difference is that the dopaminergic deficit could be partially responsible for the better improvement of RT and MT performances because sustained attention is mostly dependent on the mesocortical dopaminergic system. The lowering of dopamine concentration involves both hemispheres in our patients with Friedreich's ataxia and patients with olivopontocerebellar atrophy, but: (*a*) the dopamine pool is initially higher in the left hemisphere, thus corresponding to the right hand[42]; (*b*) the lowering of dopamine concentration in the right hemisphere, which is dominant for sustained attention, could explain why replacement therapy would improve primarily the function of the left hand.

Although the impact of AH on dopamine release[44] may explain some of its therapeutic actions, this was certainly not the only factor involved for two reasons: (1) levodopa treatment did not induce an improvement of olivopontocerebellar atrophies[45]; (2) there was no parallelism between low CSF concentrations and improvement of patients with olivopontocerebellar atrophies in a previous open study.[3]

Secondly, earlier work[21 46] has emphasised the possible role of glutamate toxicity in olivopontocerebellar atrophies. Glutamate turnover is high in the granule cell layer; granule cells, the predominant target of mossy fibres, seem to possess NMDA and at least one non-NMDA glutamate receptor. They are, therefore, able to respond to presynaptic glutamate mediated mossy fibre transmission.[46]

Thirdly, the neuronal damage associated with neurodegenerative disorders may be related to excitation of NMDA receptors.[47] It has been shown that the neurotoxicity of glutamate and closely related agonists is mediated by NMDA receptors in cultured cerebellar granule cells.[48-50]

Fourthly, memantine, an AH analogue, is a potent blocker of NMDA receptor channels.[50-52] We think that the action of AH on NMDA receptor channels provides another main explanation for the improvement found in our cases. In lurcher mutant mice, an animal model of olivopontocerebellar atrophy, amantadine and the NMDA receptor antagonist, ketamine, improved motor coordination in the coat hanger test.[53]

In summary, In this double blind clinical trial, (1) AH treatment for three to four months significantly improved some RT and MT scores (the speed of information processing, attention and motivation as well as motor performance evaluated at the level of the upper limbs only). (2) This study confirms some previous open clinical trials,[1-4] but it must be underscored that on the whole improvement was more moderate than previously reported.[4] Filla *et al*[54] found a negative effect in patients with Friedreich's ataxia receiving a single 100 mg dose of AH with ataxia scores recorded 90 minutes later. Their study is not directly comparable with the above cited investigations because of its acute nature. AH must be generally considered as replacement treatment, and its clinical action most probably requires more than 90 minutes. (3) In this short term trial, clinical improvement of motor coordination was striking in many cases of olivopontocerebellar atrophy, whereas it was mild or absent in patients with Friedreich's ataxia although their condition remained stable or was mildly improved objectively. (4) Finally, treatment with AH is justified for trial based on experimental data and the results of this study. The main difficulty with such treatments in these disorders is that neurotransmitter deficiencies are probably multifactorial.[32]

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