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A Controlled Trial of Idebenone in Huntington's Disease

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Summary: One hundred patients with clinically diagnosed Huntington's disease (HD) were randomized to either idebenone, an antioxidant and enhancer of oxidative metabolism, or placebo, in a 1-year, double-blind, parallel-group study aimed at slowing the rate of progression of the disease. Ninety-one patients completed the study. There were no significant differences between groups on the primary outcome measures of the Huntington's Disease Activities of Daily Living Scale (ADL—an index of functional status) and the Quantified Neurologic Examination (QNE). Sample size calculations based on progression of the ADL and QNE in this study group revealed that a larger study group is necessary to detect any differences less than an almost complete halting of the disease. This argues for multicenter efforts for future therapeutic trials in HD. **Key Words:** Huntington's disease—Antioxidants—Idebenone.

Huntington's disease (HD) is a degenerative neuropsychiatric disorder characterized by disturbance of movement, cognition, and emotion (1–3). It has autosomal dominant inheritance (4) and is caused by an expanded and unstable trinucleotide repeat in a gene (IT-15) on the short arm of chromosome 4 (5–7). The pathology is notable for selective neuronal vulnerability in the caudate, putamen, and deep layers of the cerebral cortex (8–15). Glutamate excitotoxicity, mediated in part through free radical production, has been implicated in its pathogenesis (12,16–20). Abnormal mitochondrial functioning has also been suggested in HD (21,22). Patients with HD and those with mitochondrial cytopathies have elevated brain levels of lactate as measured by magnetic resonance (MR) spectroscopy (23,24). Additionally, systemic injection of 3-nitropropionic acid, a mitochondrial inhibitor, replicates HD neuropathololgy in rodents (20).

While symptomatic management can provide therapeutic benefit, particularly for psychiatric aspects of the disease (25–27), there are currently no accepted specific treatments to slow the rate of clinical progression of HD. There have been two previously reported longitudinal, double-blind, placebo-controlled trials of experimental therapeutics in HD. A study of baclofen (28) showed no significant effect. A trial of *d*-α-tocopherol (vitamin E) demonstrated no overall benefit (29), but post hoc statistical analysis revealed a possible slowing of neurologic progression for early-stage patients with active drug treatment.

Idebenone is a benzoquinone derivative and has been found to act as a potent antioxidant and to protect against glutamate toxicity in animal models of HD (30) and neuronal cell lines (18). It has also been demonstrated to enhance oxidative metabolism (31–33). Idebenone has been used clinically, especially in Japan, for treatment of stroke (34–36) and generally is well tolerated without adverse effects in humans, enhancing its suitability for a therapeutic trial in HD. We therefore undertook a 1-year, placebo-controlled, double-blind, randomized, parallel-group study to test whether idebenone substantially slows the rate of progression of HD.

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METHODS

Patient Selection

The study was conducted entirely at the Johns Hopkins Hospital and was approved by the institutional review board. All patients gave informed consent. Patients were referred from the Baltimore Huntington's Disease Project (BHDP) clinic and from other general neurology clinics. Notice of the study was published in the National Huntington's Disease Society of America newsletter and several other local newsletters.

One hundred patients were entered into the study. Inclusion criteria were diagnosis of mild to moderate clinical HD as determined by positive family history, delayed onset of chorea or rigidity, and Mini-Mental State Examination (MMSE) (37) score of >14. Subjects were also required to have a relative or companion to serve as an informant and supervise medication compliance.

Exclusion criteria were current major depression, other CNS disease, active medical illnesses, use of CNS-acting medication including antipsychotics, barbiturates, benzodiazepines, CNS-acting antihypertensives, coenzyme Q, other antioxidants, or vitamin E. Standard multivitamins were allowed. Patients were told that discovery of high-dose vitamin E consumption would result in immediate withdrawal from the study. Vitamin E levels were checked to ensure that patients were not taking high doses. Because of the serious risk of depression and suicide in HD and because a significant number of HD patients become manic or seriously irritable, nortriptyline for depression and carbamazepine for mania or irritability were allowed if the medicine had not been changed within 1 month prior to screening and was not expected to change during the study period. Patients being treated with nortriptyline or carbamazepine were eligible only if they were not severely ill. Patients on nortriptyline were randomized separately. Chloral hydrate was allowed to be used up to twice a week for sleep, but not within 72 h of screening or other visits. Patients with alcohol or substance abuse or psychoses were excluded. MRI evidence of striatal infarction was also grounds for exclusion.

Evaluation at the start of the study included physical examination, chest x-ray film, electrocardiogram, thyroid function test, B_{12} and folate, and brain MR scan. Patients received as well a detailed mental status examination, along with complete blood count, blood chemistry screen, VDRL, urine analysis, and pregnancy test. Women were required to be neither pregnant, lactating, nor of childbearing capacity. Laboratory studies were monitored throughout the trial.

Outcome Measures

The primary outcome measures were the Huntington's Disease Activities of Daily Living scale (ADL), which is a functional measure (2,38,39), and the Quantitative Neurologic Examination (QNE) (40). The QNE has three subscales based on factor analysis, consisting of the Eye Movement Scale, the Chorea Scale, and the Motor Impairment Scale (MIS), which is a scale related to disturbances in voluntary movement (39). The MIS has been shown to correlate best with functional impairment (38) and degree of pathology at autopsy as measured by Vonsattel score (unpublished data from the BHDP). Furthermore, voluntary motor impairment has been shown to progress most steadily over the course of the disease (2,41). Therefore, in addition to the total scores on the scales, the MIS subscale was also prospectively analyzed. The QNE was performed by four investigators who established interrater reliability. All attempts were made to have the same individual perform the QNE at the beginning and end of the study, though this was not always possible.

The MMSE (37), along with a more detailed battery of neuropsychological tests, was also administered. All tests were carried out in double-blind fashion. The supplemental cognitive battery consisted of the following tests: the Buschke Selective Reading Test (SRT) (42; verbal learning and memory), Benton Visual Retention Test (VRT) (43; nonverbal memory), Grooved Pegboard (44; complex motor dexterity, visuomotor integration), Wechsler Adult Intelligence Scale Arithmetic subscale (45; mental arithmetic, speed of processing), Trail Making Test (46; graphomotor speed, attention, response inhibition), and Stroop Color–Word Interference Test (47; processing speed, attention, response inhibition). All tests were administered under standard instructions and scored using established standard procedures. The tests were administered in a single session on the same day as the clinical examination.

Sample Size Calculations

A study group of 100 subjects, given power = 80% and a 5% level of significance, generally is adequate to detect a difference of 0.58 SD in an out-

come measure. Based on historical longitudinal data on 49 HD subjects gathered prior to this study, with mean 1-year QNE change of 5.8 ± 10.7 and ADL 3.1 ± 5.3, our study group size could be expected to detect a substantial treatment effect that would entirely halt functional decline and improve motor function slightly.

Protocol

Patients were randomized to receive 90 mg t.i.d. of idebenone, administered as three 30-mg pills three times a day, or an equal number of placebo pills of identical appearance administered according to the same schedule. The dose used was the highest dose for which there were Phase 1 data. At this dose there were no important or frequent side effects. Patient compliance was monitored by counting of unused medication every 3 months at clinic visits. Telephone contact was made monthly. Adverse events, if any, were monitored. All scales were repeated at 6 and 12 months, but data were analyzed only for the 12-month time point.

Statistical Analysis

Intergroup comparisons (idebenone versus placebo) were made using analysis of variance for repeated measures and two-tailed *t* tests on change scores. To assess the effects of baseline values, one-way analyses of covariance (ANCOVAs) with the baseline value as the covariate were performed.

Because of the suggestion from the vitamin E trial (29) that antioxidants might have a beneficial effect in only relatively less affected patients (QNE ≤ 45), we analyzed this group separately in the current study in addition to examining the study group as a whole.

RESULTS

There were no serious adverse events associated with idebenone. Laboratory studies showed no changes, except as noted in one case described later. Seven subjects on placebo were excluded before the end of the study: four for noncompliance, one for weight loss, one for detection of a connective tissue disorder, and one for a severe depressive episode requiring pharmacologic management. Two subjects in the active drug group were excluded before the end of the study: one for noncompliance and one for mild elevation of liver function tests (who was also on nortriptyline and carbamazepine). Therefore, 91 patients (43 placebo, 48 drug) completed the full 1-year study.

Demographic information on the patients is shown in Table 1. There were no significant differences between the idebenone and placebo groups, both for the group as a whole and for those patients with baseline QNE ≤ 45, for age, age at onset, or clinical outcome measures at baseline (Table 1).

At 1 year, there were no significant differences between the drug and placebo groups on any of the clinical measures for the group as a whole (Tables 2 and 3). In every case, the ANCOVA indicated no effect of the baseline value on change scores. For the group with QNE ≤ 45, there were no differences on the primary outcome measures (QNE and ADL). A small group difference was noted for the MMSE (Table 3), but it was nonsignificant after correction for multiple comparisons. There were no significant differences on any tests in the more detailed cognitive battery for either the group as a whole or the QNE ≤ 45 group.

As there were no differences between the active drug and placebo groups, we combined the two to examine the 1-year rate of change in ADL and QNE

TABLE 1. *Demographic and baseline clinical characteristics of all 91 patients who completed study and of 63 with baseline QNE scores ≤45*

	Whole group		Baseline ≤45	
	Idebenone	Placebo	Idebenone	Placebo
No. of patients	48	43	32	31
Age (yrs)	43.9 ± 13.7	40.1 ± 9.5	42.6 ± 13.7	38.7 ± 9.7
Age at onset (yrs)	38.0 ± 13.0	35.1 ± 9.7	37.4 ± 12.8	34.5 ± 10.3
% male	44	53	41	55
ADL	11.3 ± 8.6	12.5 ± 8.6	8.6 ± 8.3	9.7 ± 7.5
QNE total	38.2 ± 15.1	36.7 ± 14.3	30.0 ± 10.4	30.0 ± 10.4
MIS	7.4 ± 3.7	7.1 ± 3.8	5.6 ± 2.8	5.6 ± 3.0
MMSE	26.0 ± 2.8	26.3 ± 2.8	26.8 ± 2.6	27.4 ± 1.9

See text for abbreviations.

TABLE 2. *Baseline and 1-yr data for whole group (idebenone vs. placebo)*[a]

	Whole group (n: idebenone = 48, placebo = 43)				
	Treatment	Baseline	1-yr	Mean change	*p*
ADL	Idebenone	11.3 ± 8.6	14.3 ± 8.6	2.9 ± 3.3	NS
	Placebo	12.5 ± 8.6	15.6 ± 8.7	3.1 ± 4.9	
QNE	Idebenone	38.2 ± 15.1	43.1 ± 15.0	4.9 ± 7.5	NS
	Placebo	36.7 ± 14.3	41.8 ± 14.6	5.1 ± 5.0	
MIS	Idebenone	7.4 ± 3.7	8.8 ± 3.9	1.4 ± 2.0	NS
	Placebo	7.1 ± 3.8	8.8 ± 4.2	1.6 ± 2.0	
MMSE	Idebenone	26.0 ± 2.8	26.1 ± 3.4	0.1 ± 2.4	NS
	Placebo	26.3 ± 2.8	25.7 ± 3.3	−0.6 ± 2.3	
Buschke SRT					
DR	Idebenone	6.3 ± 3.3	6.4 ± 2.9	0.1 ± 2.1	NS
	Placebo	5.8 ± 3.0	5.6 ± 2.8	0.2 ± 3.2	
LT	Idebenone	7.3 ± 3.2	7.3 ± 3.3	0.1 ± 3.1	NS
	Placebo	6.5 ± 3.6	6.5 ± 3.4	0.0 ± 3.0	
Benton VRT	Idebenone	7.5 ± 2.5	7.2 ± 2.6	0.1 ± 2.5	NS
	Placebo	8.0 ± 2.4	8.2 ± 2.2	0.3 ± 2.1	
Trail making					
Part A	Idebenone	69 ± 42.5	71 ± 50.8	1.8 ± 42.0	NS
	Placebo	64 ± 46.1	71 ± 52.3	6.4 ± 21.9	
Part B	Idebenone	234 ± 173.8	233 ± 182.8	2.1 ± 76.9	NS
	Placebo	214 ± 176.3	211 ± 176.5	2.7 ± 117.8	

DR, Delayed recall; LT, Long-term recall; see text for other abbreviations.
[a] Two-tailed *t* tests.

score to aid future investigations in determining sample size requirements. The overall changes in these scales over 1 year are presented in Table 4. Again, baseline value did not affect the 1-year change.

DISCUSSION

In a double-blind, placebo-controlled, randomized, parallel-group study of idebenone (Avan) in a total sample size of 91, we found no treatment effect

TABLE 3. *Baseline and 1-yr data for group with baseline QNE ≤45*[a]

	Baseline QNE ≤45 (n: idebenone = 32; placebo = 31)				
	Treatment	Baseline	1-yr	Mean change	*p*
ADL	Idebenone	8.6 ± 8.3	11.7 ± 8.5	3.2 ± 3.4	NS
	Placebo	9.7 ± 7.5	13.6 ± 8.4	3.8 ± 5.2	
QNE	Idebenone	30.0 ± 10.4	37.4 ± 13.1	7.4 ± 7.1	NS
	Placebo	30.0 ± 10.4	35.0 ± 10.3	5.0 ± 4.9	
MIS	Idebenone	5.6 ± 2.8	7.3 ± 3.5	1.7 ± 2.2	NS
	Placebo	5.6 ± 3.0	6.9 ± 3.2	1.4 ± 1.9	
MMSE	Idebenone	26.8 ± 2.6	27.3 ± 2.8	0.5 ± 2.4	<0.04
	Placebo	27.4 ± 1.9	26.8 ± 2.5	−0.6 ± 2.1	
Buschke SRT					
DR	Idebenone	7.3 ± 3.2	7.1 ± 2.7	−0.2 ± 1.9	NS
	Placebo	6.2 ± 2.9	5.9 ± 3.1	−0.4 ± 3.6	
LT	Idebenone	8.3 ± 3.1	8.2 ± 3.1	−0.1 ± 3.3	NS
	Placebo	7.1 ± 3.6	6.9 ± 3.6	−0.2 ± 3.1	
Benton VRT	Idebenone	8.0 ± 2.5	8.3 ± 2.0	0.3 ± 2.8	NS
	Placebo	8.9 ± 1.3	8.8 ± 1.5	−0.2 ± 1.6	
Trail making					
Part A	Idebenone	58 ± 34.7	55 ± 35.0	−3.2 ± 43.2	NS
	Placebo	47 ± 16.5	50 ± 18.5	2.9 ± 17.8	
Part B	Idebenone	155 ± 99.7	150 ± 109.7	−5.2 ± 59.0	NS
	Placebo	151 ± 129.6	138 ± 94.1	−13.3 ± 133.5	

DR, Delayed recall; LT, Long-term recall; see text for other abbreviations.
[a] Two-tailed *t* tests.

TABLE 4. *Baseline and 1-yr data collapsed over treatment groups*

	Baseline	1-yr	Mean change
Whole group (n = 91)			
QNE	37.5 ± 14.7	42.5 ± 14.8	5.0 ± 6.4
ADL	11.9 ± 8.6	14.9 ± 8.6	3.0 ± 4.1
Baseline QNE ≤45 (n = 63)			
QNE	30.0 ± 10.3	36.2 ± 11.8	6.2 ± 6.2
ADL	9.1 ± 7.9	12.6 ± 8.4	3.5 ± 4.4

See text for abbreviations.

on the primary outcome variables (QNE and ADL). Power analysis derived from the longitudinal data demonstrates that the study group size was adequate to detect only a large drug effect. For the group as a whole, given power = 80%, and a 5% level of significance, the sample size was adequate to detect an 80% difference in ADL (functional impairment) and QNE (neurological impairment) over 1 year. For the ≤45 group, the sample size was adequate to detect an 83% difference in ADL and 70% difference in QNE. Indeed, prestudy power analysis indicated that a statistically significant treatment effect would correspond to halting progression of disease. Therefore, this study does not test whether treatment with idebenone or similar pharmacologic agents has a smaller beneficial effect in HD. Nevertheless, it is important to note that in vivo studies indicated that idebenone was protective against striatal lesions in the rat produced by local injections of kainic acid or quisqualic acid, both of which are agonists at non-NMDA (kainate/α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid [AMPA]) glutamate ionotropic receptors. However, idebenone was not protective against local injection of quinolinic acid, an *N*-methyl-D-aspartate (NMDA) agonist (30). Given that the neuropathology of HD resembles much more closely NMDA receptor-mediated striatal neuronal degeneration than that caused by kainate/AMPA receptor agonists (19), the absence of a therapeutic effect of idebenone in HD is not inconsistent with the preclinical findings in the animal model. Furthermore, since idebenone and α-tocopherol may act at different subcellular sites (31), the negative findings of the present study do not preclude a role for oxidative damage in the pathogenesis of HD as suggested by the findings of protection with α-tocopherol treatment in early-stage HD (29).

Discussions of future therapeutic trials have focused on mild to moderately affected patients. To demonstrate a slowing of progression by 50% over 1 year in patients with QNE ≤ 45, given a power of 90% and a significance level of 0.05, using the ADL (the functional measure), one would need a total sample size of 260 subjects (130 per group), and using the QNE one would need a total sample size of 170 (85 per group). Slowing progression 25% as measured by ADL would require ~1,000 patients and by QNE ~680 patients. Shoulson et al. (28) earlier, using somewhat different measures of decline in HD, provided similar data based on analysis of the controlled trial of baclofen. Our results and those of Shoulson et al. argue for multicenter trials for promising therapeutic agents.

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