

Brief Report

Clinical Assessment of the Effect of Tetrabenazine on Functional Scales in Huntington Disease: A Pilot Open Label Study

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Abstract

Background: Tetrabenazine is a monoamine depletor with a well-documented effect against chorea associated with Huntington disease (HD). There is a paucity of data about how reduction in chorea relates to better performance on motor, gait, cognitive, and psychiatric assessments.

Methods: We designed an open label tetrabenazine withdrawal study to test performance using validated scales. The following instruments were used to assess cognitive, behavioral, and motor function in 10 patients with documented HD: The Montreal Cognitive Assessment, Beck Depression Inventory II, Dynamic Gait Index (DGI), Jebsen Hand Test, Timed 25-foot walk, Berg Balance Test (BBT), QuickDASH, and the Unified Huntington Disease Rating Scale (UHDRS) Motor, Stroop Color Word, Behavioral Assessment, Functional Checklist, and Independence Scale.

Results: Subjects performed significantly better while on tetrabenazine as measured by the DGI ($p=0.041$), BBT ($p=0.007$), and the UHDRS Total Motor ($p=0.009$), Maximum Chorea ($p=0.005$), and Stroop Color-Word tests ($p=0.028$).

Discussion: This pilot study demonstrates tetrabenazine's potential effects beyond improvement in chorea.

Keywords: Tetrabenazine, Huntington disease, chorea

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Introduction

Tetrabenazine is a monoamine-depleting drug, which was originally developed for the treatment of schizophrenia and has been successfully used for the treatment of a variety of hyperkinetic movement disorders.^{1,2} A benzoquinolizine derivative of reserpine, tetrabenazine acts by reversibly inhibiting vesicular monoamine transporter type 2 (VMAT2). The effect of tetrabenazine on reduction of chorea in Huntington disease (HD) is well documented.³ There is a paucity of data, however, on how reduction of chorea impacts motor performance and overall function, including activities

of daily living. One study, involving 13 HD patients treated with haloperidol, showed improvement of chorea but not of gait.⁴ Olanzapine treatment in HD patients showed a 35% improvement in gait, tandem gait, and pull test subscores of the Unified Huntington Disease Rating Scale (UHDRS).⁵ In another study, involving 11 patients with HD, tetrabenazine was associated with improvement in lifting of large, light objects.⁶

We designed a study to measure the functional effects of tetrabenazine on various cognitive, behavioral, and motor domains using validated scales.

Methods

Patients with a definite diagnosis of HD and on a stable dose of tetrabenazine for at least 3 months were recruited for the study from the Baylor Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC). Written informed consent, approved by the Institutional Review Board of Baylor College of Medicine, was obtained prior to commencement of the study. The enrolled patients were first evaluated within 3 hours of taking the usual, stable morning dose of tetrabenazine (ON evaluation). They were then instructed to stop taking tetrabenazine and were re-evaluated with the same battery of tests 3–4 days later (OFF evaluation), after which time their usual dose of tetrabenazine was restarted. The inclusion criteria were 1) diagnosis of definite HD by a movement disorders expert confirmed by HD gene CAG repeat length greater than 40, and 2) ability to walk independently or with minimal assistance such as with the use of a cane or walker in the ON tetrabenazine state. Patients who were non-ambulatory or required assistance to ambulate even in the ON state and those with psychiatric symptoms that would interfere with their full compliance with our instructions and testing were excluded.

After obtaining demographic information the subjects were tested using the following scales.

- 1) Montreal Cognitive Assessment (MoCA), a brief screening instrument for early cognitive impairment (range 0–30, high score=normal).⁷
- 2) Beck Depression Inventory-II (BDI-II), a validated scale of depressive symptoms (range 0–63, high score=impaired).⁸
- 3) Unified Huntington Disease Rating Scale (UHDRS), a clinical examination of motor and cognitive features commonly seen in HD (UHDRS motor range 0–124, high score=impaired, UHDRS-2 Stroop Color Word Interference calculated score, high score=normal, UHDRS-3 Behavioral Assessment frequency and severity weighted score, high score=impaired, UHDRS-4 Functional Checklist Range 0–25, high score=impaired, UHDRS-5 Independence Scale Range 0–100, high score=normal).⁹
- 4) Berg Balance Test (BBT), a 14-item assessment of sitting, standing, transferring, and turning. Each task is rated on a scale of 0–4 (range 0–56, high score=normal). This scale has been validated in the elderly population and in those with acute stroke.^{10,11}
- 5) Timed 25-foot walk (T25-FW), which consists of two timed trials of walking through a 25-foot course and was developed for the Multiple Sclerosis Functional Composite (scored as time to complete task, high score=impaired).¹²
- 6) Jebsen–Taylor Hand Function Test (JTHFT), a seven-item test designed to provide an objective measure of various aspects of hand function. Participants are timed performing common functional activities: writing, card turning (simulated page turning), picking up small common objects, simulated feeding, stacking checkers, lifting light cans, and lifting weighted cans (scored as total time to complete tasks, high score=impaired).¹³
- 7) Quick DASH, a self-report questionnaire consisting of 11 questions regarding upper extremity function (range 0–100, high score=impaired).¹⁴
- 8) Dynamic Gait Index (DGI), a gait examination that is rated on a four-point scale for each of eight conditions including stepping over an obstacle (range 0–24, high score=normal).¹⁵

Gait, hand function, and UHDRS motor assessments were performed by one of the authors (R.F.). Cognitive and psychiatric tests were performed by trained study coordinators. Each evaluation lasted approximately 90 minutes.

We applied parametric analyses to the summation of the individual ordinal scores, and non-parametric analysis using the Wilcoxon matched-pairs signed-rank test was applied for those tests whose primary measures were ordinal and those with interval-type data. Normality of distributions was tested using the Stata function *sktest*, looking at skewness and kurtosis, then both were combined. Summary data scores for each of the instruments administered were tested for equality of variance with a 95% confidence interval between the off- and on-drug state to confirm appropriateness of matched-pairs analysis. Statistical data analysis was performed using Stata/IC 11.2 for Windows (College Station, Texas). Analyses were re-run using non-parametric tests, with no difference in the outcome of significance.

Results

A total of 10 patients (60% female with a mean age of 58 ± 11 years and duration of motor symptoms for a mean of 8 ± 3.5 years) were recruited. The study was performed over a 14-month period (March 2010 to May 2011). No subjects were excluded. The average CAG repeat number for nine patients was 43 ± 2 ; one was reported to have greater than 40 CAG repeats, but the exact number was not available.

Statistically significant deterioration in BBT, DGI, and UHDRS Total Motor, Maximum Chorea, and UHDRS Stroop Color-Word scores were observed after withdrawal of tetrabenazine, suggesting that tetrabenazine treatment improves not only chorea but also gait and balance, as suggested by deterioration in BBT and DGI scores when tetrabenazine was withdrawn. No significant change was noted in other measures of function, such as JTHFT and Quick DASH, or in cognitive and behavioral measures such as MoCA and BDI-II scores (Table 1). The change in UHDRS Total Motor score (TMS) was driven by a substantial increase in the chorea scores in the OFF condition, as TMS change with chorea questions excluded was not significant ($z = -0.873$, probability $> |z| = 0.3829$).

There were no adverse events reported from withdrawal of tetrabenazine except, as expected, worsening of chorea.

Discussion

Our study showed that tetrabenazine, a VMAT2 inhibitor, has beneficial effects not only on chorea, consistent with previously published open label and randomized control studies,^{1–3} but also on gait and balance. Significantly better BBT and DGI scores with tetrabenazine suggest that improvement in chorea translates into reduced interference with the normal cadence and other components

Table 1. Study Results

| Variable | On/Off | Mean (\pm SD) | 95% CI | z^1 | Probability $> z $ |
|---|--------|------------------|-------------|--------|--------------------|
| MoCA (total) | Off | 19.95 (5.56) | 16.8–23.2 | 0.531 | 0.595 |
| | On | 20.0 (4.50) | 17.4–22.6 | | |
| Dynamic Gait Index (total) | Off | 14.4 (7.01) | 9.38–19.42 | 2.045 | 0.041 ² |
| | On | 17.5 (6.94) | 12.53–22.47 | | |
| Berg Balance Scale (total) | Off | 40.9 (9.67) | 33.99–47.81 | 2.68 | 0.007 ² |
| | On | 46.5 (6.06) | 42.17–50.83 | | |
| Jebsen Hand Test (total) (non-dominant) | Off | 193.1 (111.6) | 113.2–272.9 | 1.070 | 0.285 |
| | On | 217.3 (111.3) | 137.7–296.9 | | |
| Jebsen Hand Test (total) (dominant) | Off | 131.2 (73.3) | 78.8–183.6 | –0.459 | 0.647 |
| | On | 125.0 (57.1) | 84.1–165.8 | | |
| Timed 25-foot Walk (average, two trials) | Off | 8.5 (3.6) | 5.9–11.1 | .0153 | 0.879 |
| | On | 8.1 (2.1) | 6.6–9.5 | | |
| Beck Depression Inventory II (total) | Off | 12.8 (9.7) | 5.9–19.7 | –1.436 | 0.151 |
| | On | 10.4 (6.7) | 5.6–15.2 | | |
| QuickDASH (disability/ symptom score) | Off | 43.2 (27.5) | 23.5–62.8 | –1.02 | 0.307 |
| | On | 37.3 (26.5) | 18.3–56.2 | | |
| UHDRS-1 Motor (total motor score) | Off | 45.4 (10.4) | 38.0–52.8 | –2.609 | 0.009 ² |
| | On | 36.1 (15.7) | 24.9–47.3 | | |
| UHDRS-1 Motor (max chorea) | Off | 18.4 (2.5) | 16.6–20.2 | –2.814 | 0.005 ² |
| | On | 10.8 (5.5) | 6.9–14.7 | | |
| UHDRS-1 Motor total motor – max chorea | Off | 27.0 (9.9) | 19.9–34.1 | –0.873 | 0.383 |
| | On | 25.3 (12.4) | 16.5–34.1 | | |
| UHDRS-2 Cognition: Stroop Color-Word ²⁶ | Off | 7.72 (7.5) | .67–12.5 | 2.191 | 0.028 ² |
| | On | 14.3 (3.6) | 11.5–17.1 | | |
| UHDRS-3 Behavior: Frequency and Severity | Off | 9.3 (10.5) | 4.5–22.3 | 1.298 | 0.194 |
| | On | 13.4 (12.5) | 1.8–16.8 | | |
| UHDRS-4 Functional Checklist | Off | 15.2 (5.3) | 11.4–19.0 | 1.027 | 0.304 |
| | On | 17.0 (5.0) | 13.4–20.6 | | |
| UHDRS-5 Independence Scale | Off | 67.0(10.3) | 59.6–74.4 | | 0.062 ³ |
| | On | 74.5(13.0) | 65.2–83.8 | | |

¹Wilcoxon matched-pairs signed-rank test.²Statistically significant result.³Two tailed paired Student's t-test.

Abbreviations: CI, confidence interval; MoCA, Montreal Cognitive Assessment; SD, standard deviation; UHDRS, Unified Huntington Disease Rating Scale.

of gait and with maintenance of posture and balance. Posturography studies have shown that patients with HD are unable to properly focus on vestibular information while gating out erroneous visual and proprioceptive cues.¹⁶ Indeed, postural instability has been suggested as a marker for pre-clinical HD.¹⁷ A possible explanation for improvement of the BBT and DGI scores is improvement in gating out of abnormal sensory cues, analogous to significant improvement in gating out abnormal information in the Stroop Color Word interference test, which was also significantly improved with tetrabenazine in this sample. Improvement in Stroop performance after dopamine depletion was previously reported.¹⁸ The BBT and DGI measured not only ambulation in a straight line as the T25-FW, but also include other activities such as transferring and stepping over obstacles, which could explain the difference in significance between the T25-FW versus BBT and DGI.

We were not able to demonstrate better fine motor function with tetrabenazine. Furthermore, performance on fine motor tasks, as measured by JTHFT and Quick DASH, or speed of gait, as measured by T25-FW, may have been hampered by underlying bradykinesia, well documented in HD,¹⁹ or dysfunction in error feedback control of movements.²⁰ Depression did not improve after short-term tetrabenazine withdrawal.

Withdrawal as opposed to *de novo* study design introduces additional considerations for our study. Tetrabenazine will have “disappeared from most tissues, brain tissues included” after 24 hours.^{2,21} The active metabolite, alpha-dihydroxytetrabenazine, has a half-life of 7 hours. Based on another tetrabenazine withdrawal study, there was no statistically significant difference in chorea scores between the third and fifth day after tetrabenazine withdrawal.²² In addition, there was no significant difference in post-withdrawal chorea scores compared with baseline after 80 weeks of tetrabenazine treatment in the TETRA-HD continuation study.²³ There is the possibility of a long-term effect of tetrabenazine on histological changes in the substantia nigra²⁴ and on serotonin and alpha-1-adrenergic receptor density²⁵ as well as other pharmacological effects, which may confound our findings.²

Interpretations of the results of our study are limited because of the open label design and a small sample size. Small sample size is partly due to marked difficulties recruiting for this study as it involved withdrawal of tetrabenazine and tedious evaluation, which took several hours to complete. The presence of some placebo effect is a possibility given the open label design of the study.

Nevertheless, despite these limitations, we believe this pilot study demonstrates tetrabenazine’s potential effects beyond improvement in chorea.

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