Effect of Tetrabenazine on Motor Function in Patients with Huntington Disease

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Introduction

■ Tetrabenazine (TBZ) is a benzoquinolizine derivative which depletes dopamine within the central nervous system by reversibly inhibiting VMAT2, a presynaptic vesicular monoamine transporter. TBZ has been shown to reduce chorea related to Huntington Disease (HD) in several studies,[1-3] including TETRA-HD,[4] a multicenter double-blind placebo-controlled trial which later supported the drug's approval by U.S. Food and Drug Administration.

■ Chorea has a deleterious effect on coordinated limb movements,[5] but has little known influence on functional decline in HD.[6] In the TETRA-HD study, TBZ's beneficial effects on chorea did not produce a corresponding improvement in the UHDRS functional assessment measures, including the Total Functional Capacity (TFC) Scale, Functional Assessment Checklist (FAC), and Independence Scale (IS). Indeed, FAC scores worsened significantly when compared to controls (-6.3%, p = 0.02)

■ Accordingly, it is unclear whether and how the antichoreic effects of TBZ impact functionally relevant motor skills. For this reason, we conducted a pilot study to assess the effect of TBZ on hand function and balance.

Methods

Eleven ambulatory patients with HD were recruited from the Baylor College of Medicine Parkinson Disease Center and Movement Disorders Clinic. All participants were sufficiently disabled by chorea to justify pharmacological intervention. No individuals had used dopamine receptor blocking drugs within 30 days of enrollment. In this open-label study, all patients were assessed on two occasions within a 6 month period: (1) while off TBZ and (2) when on a stable dose of TBZ, as prescribed by the patients' treating physician (mean cumulative daily dosage 62.5±19.4 mg). The off TBZ evaluation was performed either prior to starting therapy (n=6) or following a >24 hour washout (n=5, mean washout duration 34.5±4.5 hours). All study instruments were scored as per their published guidelines.

On-off study drug evaluations included the Jebsen-Taylor Hand Function test (JTHFT),[7] Berg Balance scale (BBS),[8] a timed 25-foot walk (T25FW),[9] Montreal Cognitive Assessment (MoCA),[10] and the complete United Huntington Disease Rating Scale (UHDRS), which was video-recorded and scored by a blinded rater.[11] All patients signed an informed consent before entering the study, approved by the Baylor College of Medicine Internal Review Board for Human Research. Changes in motor performance on and off TBZ were assessed via parametric t tests and Wilcoxon signed-ranks test for not-normally distributed variables. Spearman's rho was used to assess correlations between the JTHFT and other variables including chorea scores and cognitive parameters.

Results

▪ Demographic and nonmotor characteristics of the study participants are contained in Table 1, and assessments of motor function on and off TBZ are provided in Table 2. Maximal chorea scores (UHDRS item 12) improved from 11.1±2.9 to 8.5±3.9 while on TBZ (p=0.03). There was a statistically significant improvement in large, light object lifting on the JTHFT when on TBZ, but no significant change in other JTHFT parameters or other variables on and off TBZ, including the BBS or T25FW.

▪ Scores on the JTHFT were globally slower than published normative data.[7] Of 154 JTHF assessments performed off TBZ (7 JTHFT items x 11 subjects x 2 hands), only 6.5% of dominant hand and 14.3% of nondominant hand performances were normal, i.e., within the 95 percent upper confidence limit. Performance on the JTHFT correlated with cognition, specifically the MoCA, but did not correlate with UHDRS chorea scores (Table 3).

▪ Patients reported no adverse effects related to the TBZ washout apart from increased chorea. Chronic use of TBZ was associated with mild fatigue (2 patients) and insomnia (1 patient).

Table 1 — Demographic & Nonmotor Characteristics

Age at the Evaluation	54.5 ± 13.7 [35 - 71]
Age of Symptom Onset	46.1 ± 11.7 [30 - 65]
Female gender	4 (36.4%)
Education Level (in years)	13.6 ± 4.7 [3 - 20]
Right Handedness	10 (90.9%)
CAG Repeat Length	43.1 ± 2.5 [40 - 47]
Initial Symptoms	
Motor	7 (63.6%)
Cognitive	2 (18.2%)
Psychiatric	2 (18.2%)
UHDRS - Cognitive Assessment	
Verbal Fluency Test	15.6 ± 8.1 [6 - 31]
Symbol Digit Modalities Test	17.3 ± 6.6 [7 - 28]
Stroop Interference Test - Color Naming	37.5 ± 11.2 [15 - 50]
Stroop Interference Test - Word Reading	53.2 ± 13.3 [31 - 70]
Stroop Interference Test - Interference	21.3 ± 8.1 [9 - 33]
UHDRS - Behavioral Assessment	
Mood score	6.8 ± 5.8 [0 - 16]
Behavior score	4.5 ± 4.2 [0 - 14]
Psychosis score	0.8 ± 1.9 [0 - 6]
Anxiety / Obsessiveness score	6.7 ± 6.1 [0 - 16]
UHDRS - Functional Assessments	
Functional Assessment Checklist	18.1 ± 5.1 [11 - 25]
Independence Scale	75.5 ± 10.1 [60 - 95]
Total Functional Capacity	6.5 ± 3.3 [3 - 11]
MoCA - cumulative score	19.4 ± 5.4 [7 - 24]

Table 2 — Motor Function Evaluation off and on Tetrabenazine

	Evaluation Off TBZ		Evaluation On TBZ		P-value	
UHDRS - Finger Taps	3.2 ± 1.7		3.8 ± 1.5		0.05	
UHDRS - Pronate/Supinate	2.7 ± 1.1		3.5 ± 1.7		0.04	
UHDRS - Maximal Chorea	11.1 ± 2.9		8.5 ± 3.9		0.03	
UHDRS - Motor Cumulative	29.8 ± 10.5		29.8 ± 11.2		1	
Berg Balance Scale	48.8 ± 6		49.8 ± 7.5		0.4	
25 Foot Walk	5.4 ± 1.9		5.3 ± 1.7		0.7	
Jebsen-Taylor Hand Function Test	Evaluation Off TBZ		Evaluation On TBZ		P-value	
	Dom. Hand	Nondominant	Dom. Hand	Nondominant	Dom. Hand	Nondominant
Writing	29.1 ± 15.9	75.2 ± 29.6	28.4 ± 18.1	74.1 ± 29.1	0.5	0.3
Simulated page turning	7.6 ± 2.9	8.3 ± 3.1	6.5 ± 2.5	6.9 ± 2	0.2	0.07
Lifting small, common objects	10.9 ± 4.7	10.7 ± 3.6	9.9 ± 2.7	11.1 ± 4.7	0.4	0.9
Simulated feeding	11.7 ± 3.6	16.3 ± 8.4	11.8 ± 3.9	20.6 ± 23.6	0.9	0.8
Stacking checkers	6.8 ± 3.3	7.4 ± 3.7	5.7 ± 2.1	7.3 ± 2.4	0.3	0.9
Lifting large, light objects	6.3 ± 1.4	7.5 ± 4.6	5.4 ± 1.4	5.5 ± 1.3	0.01	0.03
Lifting large, heavy objects	6.3 ± 2.8	7.7 ± 4.2	5.5 ± 1.7	6.1 ± 1.8	0.4	0.06

Table 3 — Correlation between Hand Function and the MoCA

Jebsen-Taylor Hand Function Test	*Dominant Hand*	*Non Dominant Hand*
Writing	-0.852 (0.002)	-0.432 (0.2)
Simulated page turning	-0.888 (0.001)	-0.799 (0.006)
Lifting small, common objects	-0.661 (0.04)	-0.764 (0.01)
Simulated feeding	-0.545 (0.1)	-0.669 (0.03)
Stacking checkers	-0.824 (0.003)	-0.678 (0.03)
Lifting large, light objects	-0.837 (0.003)	-0.873 (0.001)
Lifting large, heavy objects	-0.827 (0.003)	-0.706 (0.02)

Discussion

▪ Prior studies of HD have primarily utilized the UHDRS to assess functional parameters. The functional assessment portion of the UHDRS contains several cognitively demanding elements (managing finances, etc), so it is not surprising that treatment of chorea does not positively influence the UHDRS functional assessment scores.[4,12-14] Accordingly, we explored the effect of TBZ on function using scales in which patients are directly observed while performing motor tasks.

▪ In this pilot study, TBZ modestly reduced the time needed to complete tests of hand function, though the improvement only reached statistical significance in one of seven tasks.

▪ Although statistically significant, the anti-choreic effect of TBZ seen in this study was less than what was found in the only large-scale placebo-controlled trial of the drug.[4] It is unknown whether more robust control of chorea, through higher dosing, would have yielded better performance on the motor function tests that we studied.

▪ The fact that performance on tests of hand function correlates with MoCA but not UHDRS chorea scores highlights the need for additional treatments targeted toward the cognitive facets of HD.

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