Journal of the Neurological Sciences xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

# Impact of tetrabenazine on gait and functional mobility in individuals with Huntington's disease

Deb A. Kegelmeyer [a,d,*], Anne D. Kloos [a,d], Nora E. Fritz [b], Marianne M. Fiumedora [a], Susan E. White [c], Sandra K. Kostyk [a,d]

[a] The Ohio State University, School of Health and Rehabilitation Sciences, Division of Physical Therapy, United States
[b] Johns Hopkins University, Kennedy Krieger Institute, United States
[c] The Ohio State University, School of Health and Rehabilitation Sciences, Division of Health Informatics, United States
[d] The Ohio State University, College of Medicine, Neurology Department, Movement Disorders Division, United States

ARTICLE INFO

*Article history:*
Received 4 July 2014
Received in revised form 3 September 2014
Accepted 30 September 2014
Available online xxxx

*Keywords:*
Gait
Function
Mobility
Huntington's disease
Chorea
Balance

ABSTRACT

Chorea may contribute to balance problems and walking difficulties that lead to higher fall rates in individuals with Huntington's disease (HD). Few studies have examined the effects of tetrabenazine (TBZ), an anti-choreic drug, on function and mobility in HD. The purpose of this study was to compare: 1) gait measures in forward walking, 2) balance and mobility measures, and 3) hand and forearm function measures on and off TBZ. We hypothesized that use of TBZ would improve gait, transfers and hand and forearm function. Eleven individuals with HD on stable doses of TBZ were evaluated while off medication and again following resumption of medication. Significant improvements were found on the Unified Huntington's Disease Rating Scale (UHDRS) motor scores, Tinetti Mobility Test (TMT) total ($t = 4.20$, $p = 0.002$) and balance subscale ($t = -4.61$, $p = 0.001$) scores, and the Five Times Sit-to-Stand test (5TSST, $t = 3.20$, $p = .009$) when on-TBZ compared to off-TBZ. Spatiotemporal gait measures, the Six Condition Romberg test, and UHDRS hand and forearm function items were not changed by TBZ use. Improved TMT and 5TSST performance when on drug indicates that TBZ use may improve balance and functional mobility in individuals with HD.



## 1. Introduction

Chorea is a prominent and troublesome motor symptom of Huntington's disease (HD). Frequent, large amplitude choreic movements contribute to impairments in balance, walking, and daily activities, such as getting up and down from a chair, and may increase fall rates [1]. Symptomatic treatment of chorea has the potential to improve motor function, safety, and quality of life. Tetrabenazine (TBZ) is a vesicular monoamine transporter 2 (VMAT-2) inhibitor that causes a depletion of monoamines, particularly dopamine, in the brain and has been used to treat involuntary movements in a variety of movement disorders. Since the FDA approved the use of TBZ specifically for treatment of chorea in HD with orphan drug status in 2007, the use of this medication in individuals with HD has increased in the United States. Though its effect on dampening chorea is now well established, few studies of its effect on other motor and functional parameters have been undertaken.

Several neuroleptics and TBZ have been shown to decrease chorea but there are only limited studies of their effects on other motor functions in HD. The administration of the neuroleptic haloperidol to individuals affected by HD reduced chorea but showed no effects on spatial or temporal measures of gait [2,3]. Studies in a small number of individuals with HD on high doses of some atypical neuroleptics (i.e., olanzapine, zotepine) have documented improvements in chorea as well as fine motor tasks, oral functions, and some gait measures [4,5]. Following administration of TBZ for 80 weeks in 75 individuals with HD, improvements in chorea scores and in Global Improvement rating without improvement in total motor and functional measures from the Unified Huntington's Disease Rating Scale (UHDRS) were reported [6]. Gait and mobility measures were not studied in detail. However, a study of 11 individuals with HD found an association between TBZ and improved lifting of large, light objects [7] and another reported improvements in both chorea and functional measures of balance and gait (i.e., Berg Balance Scale, Dynamic Gait Index) in 10 individuals on TBZ [8]. These observations suggest that there is a need for more detailed investigations into the specific effects of TBZ administration on upper extremity function, gait and functional mobility in individuals with HD.

Previous studies evaluating TBZ in HD lacked assessment of a range of balance measures, functional tasks and quantitative changes in gait other than velocity. Therefore the purpose of this study was to compare

* Corresponding author at: The Ohio State University, 453 W. 10th Ave., 516 Atwell Hall, Columbus, OH 43210, United States. Tel.: +1 614 292 0610; fax: +1 614 292 5922.
*E-mail address:* Kegelmeyer.1@osu.edu (D.A. Kegelmeyer).

http://dx.doi.org/10.1016/j.jns.2014.09.053

performance of objective measures of mobility and function on- and off-TBZ in individuals with HD. It was hypothesized that the use of TBZ, either by improving chorea or possibly by modulating other neurological pathways, would improve 1) spatiotemporal gait parameters as measured by the GAITRite, 2) balance and/or mobility as measured by the Tinetti Mobility Test (TMT), Five Times Sit-to-Stand Test (5TSST), and Six Condition Romberg tests, and 3) function of the hand and forearm as measured by finger tapping, hand pronation/supination, and Luria (fist-hand-palm) tests (items 6–8) on the UHDRS motor scale in individuals on stable doses of TBZ. Results of this prospective open-label study will contribute to our understanding of the impact of TBZ on functional activities in the HD population.

## 2. Subjects and methods

Ambulatory individuals with a genetically confirmed diagnosis of HD, who had been maintained on a stable dose of TBZ for at least 30 days, were recruited for this study from The Ohio State University HDSA Center of Excellence. Exclusion criteria included presence of another neurologic disorder (i.e., CVA, TBI), presence of an orthopedic condition that impeded the ability to walk, pregnancy, or inability to consent to the study. Written informed consent, approved by the Institutional Review Board, was obtained from all subjects prior to enrollment.

### 2.1. Procedures

Subjects were instructed to stop TBZ on the day before testing and all subjects were off TBZ for at least 18 h prior to undergoing study tests. This ensured a period of at least 2 half-lives for metabolism of the active metabolite, alpha-dihydrotetrabenazine. Subjects arrived at the Center off-TBZ. After obtaining demographic information, the subjects were tested on the following measures:

1. The UHDRS motor scale was used to quantify motor symptoms. Items are rated on a 0–4 scale with higher scores indicating greater disability. Total motor scores (range 0–124), total chorea scores (item 7, range 0–28), and total forearm and hand function scores (items 6–8, range 0–12) [9] were calculated for each participant. The UHDRS is a commonly used outcome measure for HD clinical trials and has established reliability and validity [10].
2. Spatiotemporal parameters of walking (i.e., velocity, step and stride length and duration, percent of gait cycle in stance, swing, and double support, heel-to-heel base of support) were measured by a 16′ long GAITRite system (CIR Systems, Inc, Haverton, PA). GAITRite calculates swing percent and double support percent for each leg rather than across the entire cycle. Subjects began walking 2 m before and stopped 2 m beyond the edges of the walkway to allow for acceleration and deceleration phases. All subjects completed four separate passes across the GAITRite walking at their comfortable self-selected speed. The walks were averaged for analysis using the GAITRite software program. GAITRite measures are reliable and valid in individuals with HD [11].
3. The TMT is reliable and valid in individuals with HD and was used to measure balance, functional mobility, and fall risk [12,13]. The maximum possible score is 28 (balance subscale = 16, gait subscale = 12), with higher scores indicating better performance.
4. The FTSST assessed the subjects' abilities to balance while standing up and sitting down five times as quickly as possible from a standard armless chair. The FTSST has been shown to be a reliable and valid measure in older adults and other patient populations [14].
5. The Six Condition Romberg test was used to measure static balance. Subjects were asked to stand with arms crossed over the chest and hold each of the following stances and conditions for 30 s: 1) feet together, 2) feet together and eyes closed, 3) feet aligned in a tandem heel-to-toe position, 4) tandem position and eyes closed, 5) tandem position while counting backwards by 3's from 100, and 6) tandem position while counting backwards by 3's from 100 with eyes closed [15]. If the participant could not hold a stance for the full 30 s, the Romberg test ended at that point.

After the initial testing, the subjects were instructed to take their usual dose of TBZ. The same tests were then administered following a 2–3 hour resting period. Kenney et al. [16] documented that chorea scores begin to improve within an hour of administration of TBZ, with a mean duration of effect on chorea lasting 5.4 ± 1.3 h [16]. The majority of subjects had maximal benefit (physician rating) within 2 h of administration [16]. A neurologist with the European Huntington's Disease Network UHDRS motor rater certification administered the UHDRS motor scale. All other tests were administered by one of three physical therapist researchers who had considerable experience with test administration. Each subject was evaluated by the same tester for off- and on-TBZ tests. All subjects had practice trials of each test prior to the recorded testing to ensure understanding and to eliminate learning effects. During all gait and functional tests, subjects were guarded by one of the investigators. Safety was ensured during the off-TBZ time period by asking a family member to drive them to the testing site and by close monitoring by the investigators or family members. Previous studies have shown no significant adverse effects from the sudden withdrawal of TBZ [16,17].

All statistical analyses were performed using SPSS Version 21. All data was examined for normality using the Shapiro–Wilk Test of Normality. Accordingly, all analyses of gait and functional data were performed using paired t-tests or the Wilcoxon matched-pairs signed-rank test. A sample size of 13 participants was determined *a priori* to detect a change of 0.5 m/s in gait velocity with 95% power. To examine the variability of spatiotemporal measures of gait, coefficient of variation (CV) values were calculated for step time, stride length, swing time and double support time. Increased variability of gait measures has been associated with an increased fall risk in individuals with HD [1]. The alpha level for each test was adjusted using a Bonferroni correction.

## 3. Results

A total of fifteen individuals were recruited within a 2 year period; four subjects were excluded due to a previously undocumented history of a mild CVA ($n = 1$), an inability to participate in follow-up testing due to family issues ($n = 2$), and an elected termination of the medication ($n = 1$). Eleven ambulatory individuals with HD [mean age ± SD (range) = 52.2 ± 10.0 (33–69 years); 9 women; mean time since symptom onset = 8.1 ± 5.7 (2.5–21 years); mean CAG repeat size = 44.6 ± 1.6 (41–51)] completed the study. All subjects historically had chorea scores >10 before starting on TBZ. The average daily dosage of TBZ was 64.7 ± 20.8 mg with a range of 37.5 mg to 100 mg. All other medications taken by subjects were stable during the month prior to testing. In addition, none of the subjects or caregivers reported deviation from their usual daily activities or initiation of any new exercise regimen in the month preceding the testing.

Tetrabenazine use was associated with significant improvements in mean UHDRS total motor scores [off-TBZ = 55.27 ± 12.09 (32–78) and on-TBZ = 47.73 ± 12.51 (27–69); $p = .001$] with the change in total motor scores driven primarily by the increase in the chorea scores in the off state [chorea scores off-TBZ = 17.09 ± 3.3 (13–25) and on-TBZ = 12.91 ± 2.8 (10–19)]. However, total motor scores excluding chorea measures of the face, trunk, upper extremity and lower extremity [off-TBZ = 38.18 ± 11.03 (19–61) and on-TBZ = 34.82 ± 11.50 (17–58)] were also still significantly better ($p = .008$) on TBZ.

Spatiotemporal parameters of gait including CVs remained stable in the on-TBZ and off-TBZ conditions (Table 1). Gait parameters of the left and right leg were also compared and showed no significant differences side to side. Subjects exhibited significantly better TMT total and balance subscale scores ($p = .002$; 10/11 participants' scores were improved) and FTSST scores ($p = .009$; 9/11 participants had faster

Please cite this article as: Kegelmeyer DA, et al, Impact of tetrabenazine on gait and functional mobility in individuals with Huntington's disease, J Neurol Sci (2014), http://dx.doi.org/10.1016/j.jns.2014.09.053