Short-Term Effects of Tetrabenazine on Chorea Associated with Huntington Disease

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ABSTRACT

OBJECTIVE: We sought to assess the short-term clinical effects of tetrabenazine (TBZ) on choreic movements in Huntington disease patients.

METHODS: A total of 10 patients on stable doses of TBZ were enrolled in this observational study. Patients took their evening dose of TBZ and presented the next day to the Baylor College of Medicine Movement Disorders Clinic without taking the usual morning dose. They were assessed using the Unified Huntington Disease Rating Scale (UHDRS) motor assessment and Beck Depression Inventory (BDI). The usual morning dose of TBZ was then administered and patients were followed with serial UHDRS motor examinations approximately every 2 hours until choreic movements subsided and then returned.

RESULTS: TBZ decreased the UHDRS chorea score on average 42.4 ± 17.8%. The duration of effect varied from a minimum of 3.2 hours to a maximum of 8.1 hours (mean = 5.4 ± 1.3). No patient experienced an adverse event related to TBZ or its withdrawal.

CONCLUSIONS: During short-term follow up after a single dose, TBZ improves chorea for approximately 5 hours.

INTRODUCTION

Tetrabenazine (TBZ), a monoamine-depleting drug synthesized nearly 50 years ago, inhibits monoamine uptake into granular vesicles of presynaptic neurons through its ability to bind to vesicular monoamine transporter 2 (VMAT2). Though initially designed as an antipsychotic medication, clinicians primarily use TBZ to treat a variety of hyperkinetic movement disorders such as chorea, tics, and tardive dyskinesia. TBZ ameliorates chorea related to Huntington disease (HD) and other etiologies. In published clinical trials, the dose of TBZ is usually titrated to "best dose," defined as the dose that provides efficacy without intolerable side effects. TBZ, however, displays considerable inter-individual variability with regard to "best dose"; some patients respond to doses as low as 12.5 mg/day, whereas others require up to 400 mg/day. For a given individual, the therapeutic window for TBZ is quite narrow. Dose-limiting side effects include sedation, parkinsonism, akathisia, and depression.

METHODS

- **All patients met clinical criteria for HD and were sufficiently disabled by chorea to justify pharmacologic intervention.**
- **Stable TBZ dosing was a requirement for inclusion in the study.**
- **Patients took their last regular dose of TBZ the evening prior to the observation day. At least 12 hours intervened between the last dose and the baseline evaluation.**
- **One rater (CK) completed all clinical evaluations. Baseline data consisted of the motor portion of the Unified Huntington Disease Rating Scale (UHDRS) and the Beck Depression Inventory (BDI).**
- **Each patient then took their usual morning dose of TBZ followed by serial assessments of the UHDRS motor score every 90-150 minutes. A total of at least 4 serial assessments were completed until reemergence of baseline chorea indicated wearing off of TBZ benefit.**
- **The maximal decrease in UHDRS chorea score was calculated by the following equation:**

$$\frac{\text{Baseline UHDRS chorea score} - \text{Lowest UHDRS chorea score}}{\text{Baseline UHDRS chorea score}}$$

- **Duration of effect was defined as the time needed for the chorea score of the UHDRS motor assessment to return to baseline from the time of TBZ administration.**
- **To calculate duration of effect in four patients whose chorea score did not return to the baseline value, the return-to-baseline time values were normalized by linear extrapolation of the final two time-points relative to the baseline UHDRS chorea score.**

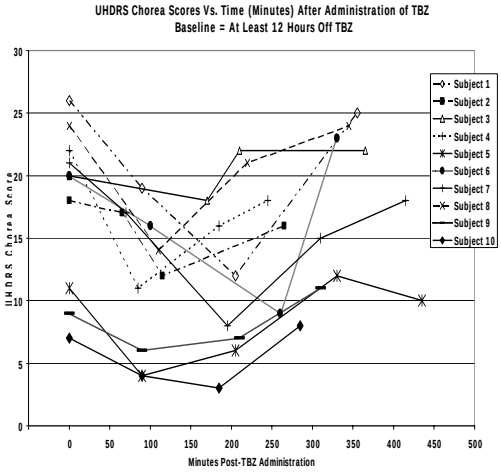
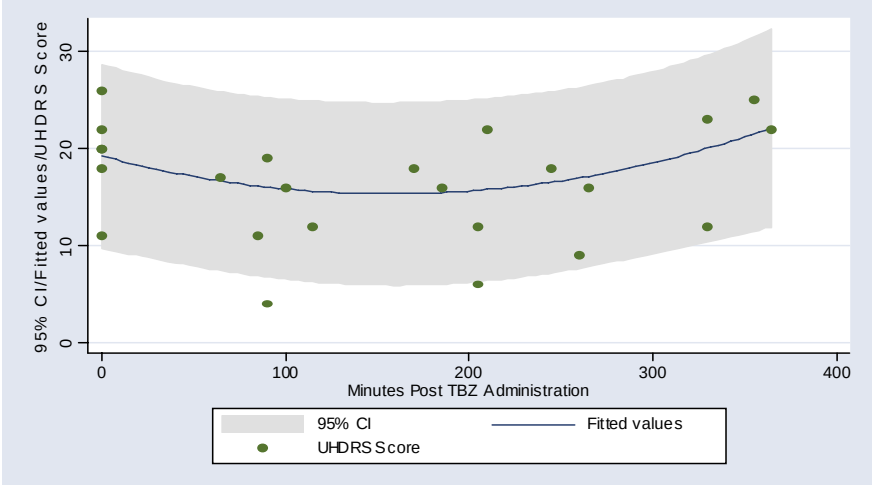


Table 1. Demographic Information

Subject Number	Age (year)	Gender (M/F)	Duration of Disease (yr)	CAG Repeats	TBZ dose (mg/day)	Baseline UHDRS	Baseline BDI
1	48	F	10	45	37.5	83	5
2	64	M	24	41	75.0	44	5
3	59	M	10	42	175.0	84	10
4	62	M	9	41	75.0	57	15
5	67	F	14	41	50.0	35	18
6	35	M	5	52	150.0	51	1
7	71	F	12	43	75.0	88	7
8	41	M	11	47	175.0	62	6
9	55	F	5	43	37.5	19	4
10	61	M	4	42	50.0	24	12
Mean (SD)	56.3 (11.6)	N/A	10.4 (5.8)	43.7 (3.5)	90.0 (55.2)	54.7 (24.9)	8.3 (5.3)



RESULTS

- ✓**The 10 patients (6 males) had a mean age of 56.3 ± 11.6 years and a mean duration of symptoms of 10.4 ± 5.8 years (Table 1).**
- ✓**Daily TBZ dosage ranged from 37.5 to 175.0 mg/day (mean = 90.0 ± 55.2).**
- ✓**The baseline UHDRS and BDI scores were 54.7 ± 24.9 and 8.3 ± 5.3, respectively.**
- ✓**Based on the rated perceptual intensity change of one rater, the UHDRS chorea score decreased by 42.4% ± 17.8 with a tendency to improve (decrease) and then worsen (increase) over several hours (Figure 1).**
- ✓**The mean duration of effect equaled 5.4 ± 1.3 hours.**

CONCLUSIONS

- **To our knowledge, this is the first report of short-term clinical effects of TBZ on chorea associated with HD.**
- **Clinical benefits at a given dose of TBZ can be assessed rapidly in most patients.**
- **The mean duration of TBZ effect on chorea equaled 5.4 ± 1.3 hours.**
- **This duration of action necessitates dosing three times per day in most patients.**

REFERENCES

1. Paleacu D, Giladi N, Moore O, et al. Tetrabenazine treatment in movement disorders. Clin Neuropharmacol 2004;27:230-233.
2. Kenney C, Jankovic J. Tetrabenazine in the treatment of hyperkinetic movement disorders. Expert Rev Neurother 2006;6:7-17.
3. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology 2006;66:366-372.
4. Frank S, Ondo WG, Hunter C, et al. A randomized, double-blind, placebo-controlled, staggered withdrawal study in patients with Huntington's disease treated with tetrabenazine. Ann Neurol 2006;(in press).
5. Ondo WG, Tintner R, Thomas M, et al. Tetrabenazine treatment for Huntington's disease-associated chorea. Clin Neuropharmacol 2002;25:300-302.
6. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997;48:358-362.
7. Chatterjee A, Frucht SJ. Tetrabenazine in the treatment of severe pediatric chorea. Mov Disord 2003;18:703-706.
8. Pettibone DJ, Totaro JA, Pflueger AB. Tetrabenazine-induced depletion of brain monoamines: characterization and interaction with selected antidepressants. Eur J Pharmacol 1984;102:425-430.
9. Quinn GP, Shore PA, Brodie BB. Biochemical and pharmacological studies of RO 1-9569 (tetrabenazine), a nonindole tranquilizing agent with reserpine-like effects. J Pharmacol Exp Ther 1959;127:103-109.
10. Scherman D. Dihydrotetrabenazine binding and monoamine uptake in mouse brain regions. J Neurochem 1986;47:331-339.

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