Clinical Neuropharmacology
Vol. 25, No. 6, pp. 300–302

Tetrabenazine Treatment for Huntington's Disease-Associated Chorea

William G. Ondo, Ron Tintner, Madhavi Thomas, and Joseph Jankovic

Department of Neurology, Baylor College of Medicine, Houston, Texas, USA

Summary: Tetrabenazine (TBZ), a monoamine depleter and dopamine receptor blocker, is used to treat a variety of hyperkinetic movement disorders. The objective was to study the efficacy and tolerability of TBZ for chorea associated with Huntington's disease (HD). Nineteen patients (12 female), mean age 56.3 ± 12.4 years (range 37–76 years) diagnosed with HD were prospectively evaluated at initial and follow-up visits using a modified Abnormal Involuntary Movement Scale (AIMS). Patients were videotaped, and the randomized videotapes were rated with the motor subset of the AIMS by two investigators who were blinded to treatment assignment. Eighteen patients completed and were rated after 5.9 ± 3.3 months (range 2–11) at a final mean TBZ dose of 62.5 ± 37.4 mg/day (range 25–150). The blinded videotaped motor scores showed that 15 were better on TBZ, 2 were better before TBZ, and 1 was unchanged ($p < 0.001$, Wilcoxon signed rank test). The mean score improved from 16.2 ± 4.8 to 12.8 ± 4.4. Adverse events included akathisia, insomnia, constipation, depression, drooling, and subjective weakness. All 18 of these patients have continued to take TBZ since completion of the study. TBZ was well tolerated and resulted in a significant improvement in modified AIMS scores in HD patients. These results support the use of TBZ for chorea in patients with HD. **Key Words:** Huntington's disease—Tetrabenazine—Chorea

Tetrabenazine (TBZ) inhibits presynaptic dopamine release and blocks postsynaptic dopamine receptors. It has been used for decades to treat a variety of hyperkinetic movement disorders, including Huntington's disease (HD) (1–12). Nevertheless, relatively little controlled data have been reported. Furthermore, as a result of marketing and financial factors, the drug remains largely unavailable in the United States. We conducted a blinded trial comparing randomized videotapes to test the efficacy of TBZ for the treatment of HD associated chorea.

METHODS

Patients diagnosed with HD, who reported disability specifically due to chorea, were recruited from the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders. Many patients were refractory to other medical treatments, but this was not a specific inclusion criteria. The diagnosis of HD was confirmed by expanded CAG repeat testing in 17 patients and based on a typical clinical presentation with positive testing in other family members in 2. Tetrabenazine was obtained from the supplier (Cambridge Laboratories, London, UK) under one of the authors' (J.J.) claimed Investigational Exemption for a New Drug (IND).

Patients underwent neurologic history and examination, and signed informed consent forms. They were videotaped while sitting (whole body and facial close-up), talking, arms forward, and walking (approximately 3 minutes). Tetrabenazine was then started at a dose of 12.5 mg twice daily (25 mg/day) and titrated up to a maximum of 50 mg three times a day (150 mg/day) in weekly increments. Patients were instructed to stop increasing the dose if they experienced satisfactory benefit at their current dose and/or if adverse events (AE) became troublesome. Patients were not allowed to change any other medicines during the study period. They were asked to return in approximately 4 months,

Address correspondence and reprint requests to Dr. William Ondo, 6550 Fannin, Suite 1801, Houston, TX 77030, USA. E-mail: wondo@bcm.tmc.edu.

but this varied due to geographic constraints. During their re-evaluation, patients underwent global assessments (including caregiver input), AE assessments, neurologic examinations, and repeat videotaping. Any AE experienced during titration or at the clinic visit were reported.

Upon completion of enrollment, the videotapes were edited, randomized, and coded. Two separate investigators (M.T., R.T.) who were not otherwise involved with patient management and who were blinded to treatment assignment rated the pre-TBZ and post-TBZ videos using the motor section of the AIMS (questions 1–7) (13). The mean of the two scores was used for statistical analysis. Audio was not allowed, as this could have jeopardized blinding in several cases.

Patient evaluations included the video randomized blinded motor subscore (1–7) of the AIMS, global impressions, and AE. The Wilcoxon signed rank test was used to compare pretreatment and posttreatment scores.

RESULTS

Nineteen patients (12 female), age 56.3 ± 12.4 (range 41–76 years) were enrolled. One patient was lost to follow-up and is not otherwise included in the analysis. Patients had a mean of 43.0 ± 2.6 CAG repeats and had an 8.1 ± 5.3-year duration of HD symptoms (Table 1). The initial symptoms were chorea (10), psychiatric (5), balance difficulties (2), and loss of dexterity (1). The Mini Mental Status Examination (MMSE) at entry into the study averaged 24.5 ± 3.8. Thirteen of the 19 patients had tried 21 total medications specifically for chorea prior to study entry. None of the medications were felt to be satisfactory to the patient.

The patients were subsequently evaluated 5.9 ± 3.3 months (range 2–11) after starting TBZ at a mean final dose of 62.5 ± 37.4 mg/d (range 25–150). Twelve patients divided their total dose into three doses per day, and six patients took two doses per day. Patients subjectively rated themselves as markedly improved (7), moderately improved (7), mildly improved (3), and unchanged (1). No patient who completed the evaluation felt that his or her condition had worsened. The blinded videotaped motor subscores showed that 15 patients improved on TBZ, 2 were better before TBZ, and 1 was unchanged ($p < 0.001$, Wilcoxon signed rank test). The mean motor AIMS score improved from 16.2 ± 4.8 to 12.8 ± 4.4. Adverse events included akathisia (3), insomnia, constipation, depression, drooling, and subjective weakness. No patient complained of motor slowing or any other Parkinsonian symptom. All AE, except one case of akathisia, which improved immediately upon reduction of the dose, were rated as mild. All 18 patients have continued to take TBZ since completion of the study.

DISCUSSION

We report a single blinded trial of TBZ for the management of chorea in 18 patients with HD. In our population, TBZ was an effective and well-tolerated treatment.

Our results concur with those of open-label (1–9)

TABLE 1. *Patient demographics and treatment responses*

Sex	Age	Duration of HD SX (years)	CAG repeat	TBZ dose (mg/day)	Previous chorea medicines	Subject response	Pre-TBZ aims	Post-TBZ aims	Delta aims
F	42	3	46	25	tram	Moderate	11	8	3
F	49	9	46	37.5		Marked	17.5	10.5	7
M	66	8	41	25	hal, narc	Moderate	15	12	3
M	55	17	42	75	hal	Marked	28	18	10
F	76	8	41	37.5	ris, hal, bac, alp	None	21.5	19	2.5
M	40	20		150		Moderate	22	20.5	1.5
F	58	2	43	75	ris	Mild	12.5	9	3.5
F	73	6	40	75	hal, clon	Marked	16.5	11.5	5
F	62	12	43	50	flu	Mild	22	18.5	3.5
M	60	4		75	clon	Moderate	15.5	7.5	8
M	46	1	42	75		Marked	8.5	13	−4.5
F	69	9	41	50		Moderate	13.5	14	−0.5
F	55	13	43	150	alp, val	Marked	15.5	5.5	10
F	47	8	42	75	flu, lor	Moderate	16	14	2
F	41	3	44	50		Mild	16.5	16.5	0
M	72	3	40	25		Mark	11	9.5	2.5
F	65	13	44	50	flu	Moderate	12	9	3
F	37	6	50	25	val	Mark	16.5	15	1.5
mean	56.2	8.1	43.0	62.5			16.2	12.8	3.3
s.d.	12.4	5.3	2.6	37.4			4.8	4.4	3.6

alp = alprazolam, bac = baclofen, clon = clonidine, flu = fluphenazine, hal = haloperidol, lor = lorazepam, narc = various narcotics, ris = risperidone, tram = tramadol, val = valproate

and smaller, partially controlled and controlled trials (10–12). Tetrabenazine also compares favorably to other medications used to treat HD chorea (10–12) and has been reported to have synergistic effects when used in combination with the dopamine antagonist pimozide. (14) Furthermore, long-term data suggests that its benefit persists for a longer duration when used for HD compared to other hyperkinetic disorders (1,9).

Adverse events were mild but generally similar to those previously documented. Specifically, no patient became Parkinsonian, and only one patient felt that mood worsened. This likely resulted from the relatively low doses used in our flexible dosing schedule. Patients with Huntington's disease may also be less likely to experience typical TBZ associated AE because they have chorea, which intuitively lessens the risk of drug-induced Parkinsonism, and they are middle aged, rather than at age extremes. In our experience, that age group has the fewest AE. Tetrabenazine has never been reported to cause tardive dyskinesia (TD). This is particularly important because HD patients may be predisposed to develop TD with typical dopamine antagonists (12).

Tetrabenazine, a benzoquinolizine derivative, depletes presynaptic dopamine, norepinephrine, and serotonin storage and antagonizes postsynaptic dopamine receptors. Oral absorption is relatively poor and erratic (15,16). The serum half-life after oral ingestion is approximately 6 hours, but this is also highly variable (15,16). The drug subsequently undergoes first-pass metabolism to dihydrotetrabenazine (DTBZ), which appears to have similar pharmacologic activity. Serum levels of this compound are much higher than the parent compound, it is less protein bound, and the half-life is consistently around 10 hours. Therefore, it is possible that most of the clinical effects result from DTBZ. Individual response may also depend upon specific monoamine transporter types. (17)

Potential shortcomings of our clinical design include the limitations of video rating, which tend to blunt subtle differences in movement. The chorea in HD is also variable and influenced by the immediate surroundings. Our experience is that HD patients generally show less chorea when knowingly videotaped. This could lessen differences in the motor examinations and possibly weaken our results. The AIMS scale was predominately designed to evaluate TD and therefore may under-represent extremity movements relative to facial movements, again possibly blunting apparent efficacy. Our patients were largely referred from other neurologists after failing conventional treatment and therefore may be biased toward more severe cases. We only evaluated chorea and only in HD patients for whom it was a major feature of their disease. Chorea, however, represents only one feature of HD, and this may not be the major cause of disability. Therefore, these results should not be extrapolated to suggest that TBZ helps all HD patients. Finally, this was not a placebo-controlled trial.

Nevertheless, given the fairly consistent benefit and good tolerability shown in this study, we feel that TBZ should be considered for the symptomatic treatment of chorea in HD.

REFERENCES

1. Jankovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. *Neurology* 1988;38:391–94.
2. Toglia JU, McGlamery M, Sambandham RR. Tetrabenazine in the treatment of Huntington's chorea and other hyperkinetic movement disorders. *J Clin Psychiatr* 1978;39:81–87.
3. Godwin-Austen RB. The treatment of the choreas and athetotic dystonias. *J R Coll Physicians Lond* 1979;13:35–38.
4. Dalby MA. Effect of tetrabenazine on extrapyramidal movement disorders. *Br Med J* 1969;2:422–23.
5. Huang CY, McLeod MLG, Holland RT, et al. Tetrabenazine in the treatment of Huntington's chorea. *Med J Aust* 1976;1:583–84.
6. Kingston D. Tetrabenazine for involuntary movement disorders. *Med J Aust* 1979;1:628–30.
7. Soutar CA. Tetrabenazine for Huntington's chorea. *Br Med J* 1970; 4:55.
8. Asher SW, Aminoff MJ. Tetrabenazine and movement disorders. *Neurology* 1981;31:1051–54.
9. Jankovic J, Beach J. Long term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology* 1997;48:358–62.
10. Swash M, Roberts AH, Zakko H, et al. Treatment of involuntary movement disorders with tetrabenazine. *J Neurol Neurosurg Psychiatry* 1974;35:186–91.
11. McLellan DL, Chalmers RJ, Johnson RH. A double-blind trial of tetrabenazine, thiopropazate, and placebo in patients with chorea. *Lancet* 1974;1:104–107.
12. Gimenez-Roldan S, Mateo D. Huntington disease: tetrabenazine compared to haloperidol in reduction of involuntary movements. *Neurologia* 1989;4:282–87.
13. ECDEU Assessment Manual for Psychopharmacology. Guy W, ed. Washington, D.C.: U.S. Department of Health Education Welfare, 1976:534–37.
14. McArthur AW, Pollock M, Smidt N, et al. Combined therapy with tetrabenazine and pimozide in Huntington's chorea. *N Z Med J* 1976;83:114–16.
15. Mehvar R, Jamali F, Watson MW, et al. Pharmacokinetics of tetrabenazine and its major metabolite in man and rat. Bioavailability and dose dependency studies. *Drug Met Disp* 1987;15:250–55.
16. Roberts MS, McLean S, Millingen KS, et al. The pharmacokinetics of tetrabenazine and its hydroxy metabolite in patients treated for involuntary movement disorders. *Eur J Clin Pharmacol* 1986;29: 703–708.
17. Peter D, Vu T, Edwards RH. Chimeric vesicular monoamine transporters identify structural domains that influence substrate affinity and sensitivity to tetrabenazine. *J Biol Chem* 1996;271:2979–86.