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Viewpoint

Short-Term Effects of Tetrabenazine on Chorea Associated With Huntington's Disease

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Abstract: We sought to assess the short-term clinical effects of tetrabenazine (TBZ) on choreic movements in Huntington's disease patients. 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's Disease Rating Scale (UHDRS) motor assessment and Beck Depression Inventory. 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. 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. During short-term follow-up after a single dose, TBZ improves chorea for approximately 5 hours. © 2006 Movement Disorder Society

Key words: Huntington's disease; tetrabenazine; chorea

Tetrabenazine (TBZ), a monoamine-depleting drug synthesized nearly 50 years ago, inhibits monoamine uptake into granular vesicles of presynaptic neurons[1,2] through its ability to bind to vesicular monoamine transporter 2 (VMAT2).[3] 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's disease (HD) and other etiologies.[4–10] 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 interindividual 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.[9] For a given individual, the therapeutic window for TBZ is quite narrow. Dose-limiting side effects include sedation, parkinsonism, akathisia, and depression.

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PATIENTS AND METHODS

Patients were recruited from the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC) at the Baylor College of Medicine (BCM), Houston, Texas, after giving a written informed consent approved by the BCM Institutional Review Board. All patients met clinical criteria for HD and were sufficiently disabled by chorea to justify pharmacological intervention. Patients also displayed the characteristic expansion of 40 or more CAG repeats in the *huntingtin* gene. 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 eval-

TABLE 1. *Demographic information (n = 10)*

Subject number	Age (yr)	Sex	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

Baseline, no tetrabenazine for 12 or more hours.

uation. One rater (C.K.) completed all clinical evaluations. Baseline data consisted of the motor portion of the Unified Huntington's 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 to 150 minutes. A total of at least four serial assessments were completed until reemergence of baseline chorea indicated wearing *off* of TBZ benefit.

Demographic data were prepared in tabulated form. The maximal decrease in UHDRS chorea score was calculated by the following equation: (baseline UHDRS chorea score − lowest UHDRS chorea score)/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.

RESULTS

The 10 patients (6 male) 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 (Fig. 1, Table 2). The mean duration of effect equaled 5.4 ± 1.3 hours.

DISCUSSION

The medical literature provides robust evidence that TBZ improves chorea for several weeks, months, and even years.[4–10] The Huntington Study Group recently completed a phase III study assessing the safety, efficacy, and dose tolerability of TBZ for ameliorating chorea in patients with HD (TETRA-HD).[6] A total of 84 patients were randomized to placebo (n = 30) or TBZ (n = 54) up to 100 mg/day. Patients in the treatment arm were administered increasing doses of 12.5 mg/week. After 12 weeks, all treatment was discontinued and patients returned 1 week later for the final study visit. Based on the chorea score of the

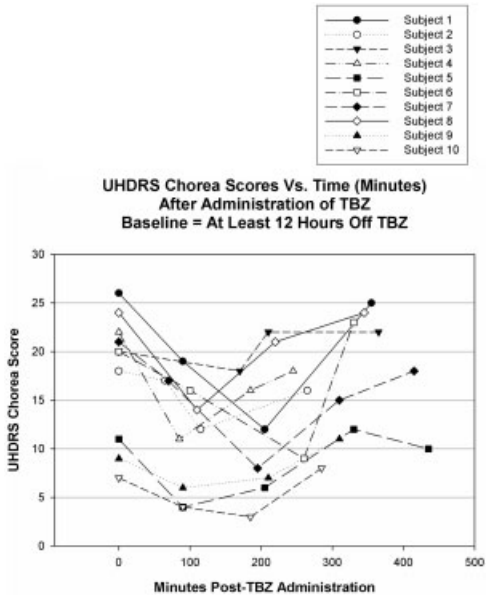

FIG. 1. Summary of Unified Huntington's Disease Rating Scale Chorea Subscale over time (n = 10).

TABLE 2. *Summary of UHDRS scores*

Subject number and time (min)	UHDRS chorea	UHDRS total
1		
0	26	83
90	19	70
205	12	60
355	25	72
2		
0	18	44
65	17	39
115	12	36
265	16	39
3		
0	20	84
170	18	78
210	22	73
365	22	75
4		
0	22	57
85	11	40
185	16	47
245	18	51
5		
0	11	35
90	4	26
205	6	28
330	12	34
435	10	32
6		
0	20	51
100	16	49
260	9	41
330	23	55
7		
0	21	88
70	17	74
195	8	69
310	15	76
415	18	85
8		
0	24	62
110	14	47
220	21	60
345	24	64
9		
0	9	19
90	6	15
210	7	15
310	11	19
10		
0	7	24
90	4	17
185	3	16
285	8	22

T = 0: baseline.

UHDRS, TBZ was found to reduce chorea significantly. Likewise, the Clinical Global Impression of Change improved significantly more in patients treated with TBZ when compared to placebo.

A review of the medical literature reveals little information regarding the pharmacokinetics and pharmacodynamics of TBZ. The metabolism of TBZ in humans, dogs, and rabbits was first described in 1966 by Schwartz and colleagues,[11] based on urinary analysis yielding evidence of a TBZ metabolite with two stereoisomers. One investigator found no evidence of unchanged TBZ in the urine of four patients indicating extensive metabolism with linear kinetics in the range studied (37.5 to 112.5 mg/day).[12] Another study concluded that TBZ displays variable interindividual half-life and a relatively low bioavailability.[13] Published PET scan studies conducted in rodents, primates, and humans confirm that TBZ and its active metabolite cross the blood–brain barrier and concentrate mainly in the basal ganglia.[14–16]

In light of this limited pharmacokinetic data, we sought to evaluate the clinical effects of TBZ on 10 patients during several hours of observation. To our knowledge, this is the first report on the short-term clinical effects of TBZ on chorea-associated HD. The major limitations of this study relate to its open-label design, the lack of a control group, and no pharmacokinetic data. Nevertheless, this study supports the efficacy of TBZ in the treatment of chorea with a variable interindividual duration of effect lasting approximately 5 hours. The observed duration of action necessitates dosing three times per day in most patients. Finally, the potential clinical benefits at a given dose can be assessed rapidly in most patients.

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