Tetrabenazine for the Treatment of Chorea

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Abstract

Objective: To describe long-term experience with tetrabenazine (TBZ) in the treatment of chorea.

Background: Dopamine receptor blocking drugs (DRBD), also known as neuroleptics, commonly used in the treatment of involuntary movements may cause potentially serious adverse effects, including tardive dyskinesia (TD). This side effect of DRBD has not been reported with TBZ, a synthetic benzo-quinolizine that acts as a monoamine-depleting drug by inhibiting central vesicular monoamine transporter type 2 (VMAT2). TBZ has been reported to have an ameliorating effect in a variety of hyperkinetic movement disorders, including TD, Tourette syndrome, Huntington disease (HD), and other involuntary movement disorders, but the drug has not yet been approved for the treatment of these disorders in the United States. Marked improvement in chorea, without serious adverse events, was reported in 83% of the first 90 patients treated between 1980 and 1995 at the Parkinson's Disease Center and Movement Disorders, Baylor College of Medicine (Jankovic J, Beach J. Neurology 1997;48:358-362).

Design/Methods: A retrospective chart review was performed on subjects treated with TBZ between January 1997 and January 2004. Response to treatment was assessed by a previously published response scale (1 = marked reduction in abnormal movements, excellent improvement in function; 4 = poor or no response; 5 = worsening) (Jankovic and Beach, 1997). All adverse events were captured and coded according to their relationship to the study drug.

Results: To date, 165 patients (67 males) with chorea have been treated with TBZ at Baylor College of Medicine. Of the 98 patients (age: 53 ± 19 years; range: 3 – 80) with evaluable visits since 1997, 68 had HD and the remainder had other choreas. Over 80% of the patients experienced robust improvement (rating of 1 or 2) in their chorea. The most frequent adverse effects, all of which were dose-related and none were permanent, included drowsiness or fatigue, depression, and akathisia. No patient experienced orthostatic hypotension or tardive dyskinesia.

Conclusion: TBZ is a safe and effective drug for chronic treatment of chorea associated with HD or other disorders.

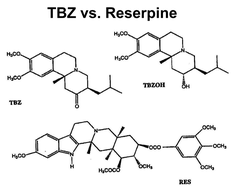
Introduction

Tetrabenazine (TBZ) is a synthetic benzo-quinolizine that acts as a monoamine-depleting drug by inhibiting central vesicular monoamine transporter type 2 (VMAT2). [Figure 1 and Table 1] While the VMAT1 gene is localized on Chr 8 (8p21.3) and the VMAT2 gene on Chr 10 (10q25), only VMAT2 is expressed in the human brain. Furthermore, the higher selectivity of TBZ for hVMAT2 by a factor of 10^4 over hVMAT1 explains the CNS-selective effects of the drug.

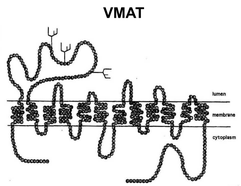
Over a thousand patients suffering from hyperkinetic movement disorders have been treated with TBZ at the Parkinson's Disease Center and Movement Disorders Clinic at Baylor College of Medicine since we received Notice of Claimed Investigational Exemption for a New Drug (IND) in March of 1979. Our initial double-blind, placebo-controlled, study involving patients with a variety of hyperkinetic movement disorders showed that the drug was well tolerated and its efficacy was superior to placebo (Jankovic J. Ann Neurol 1982; 11:41-47). In 1997 we described our open label experience in 400 patients (Jankovic J, Beach J. Neurology 1997;48:358-362). In 90 patients with chorea the response rate was high, with 83% of patients having marked improvement of chorea.

Figure 1. Tetrabenazine (TBZ)
Vesicular Monoamine Transporter (VMAT)

TBZ vs. Reserpine



VMAT



Methods

Patients included in this open-label study had DNA-verified HD or other forms of chorea, other than drug-induced chorea (e.g. TD) in whom the chorea interfered with functioning and was not satisfactorily controlled with conventional therapy. After signing an informed consent, approved by the Baylor Institutional Review Board, all patients were videotaped according to a standardized protocol. They were subsequently followed every three to six months at which time their response was assessed using a 1 to 5 response rating (1 = marked reduction in abnormal movements, excellent improvement in function; 4 = poor or no response; 5 = worsening) (Jankovic J, Beach J. Neurology 1997;48:358-362). TBZ adverse events were captured by an open-ended question ("have you noted any new symptoms since last visit"). This was followed by specific questions related to level of alertness, mood and motor function. The patients were also examined for any evidence of parkinsonism. For each adverse event the investigator assigned a level of relationship to TBZ as either probable, possible, or unlikely. In addition, adverse events were categorized as "not severe" or "severe". Complete blood counts and liver function tests were screened at least once a year. For the purpose of this analysis, patient data was extracted from the clinic and hospital records onto Case Report Forms (CRFs) and then entered into a database. The completeness and accuracy of the entered data was verified by an independent audit of about 25% of the records.

Table 1. Tetrabenazine Versus Reserpine

Pharmacological Properties	Tetrabenazine	Reserpine
Mechanism of Action	Selectively binds hVMAT2 (CNS)	Binds hVMAT1 (PNS) & hVMAT2 (CNS)
	Reversibly binds VMAT2	Irreversibly binds VMAT
	Binds intravesicular site	Binds cytoplasmic site
Peripheral monoamine depletion	No	Yes
Duration of action in humans	Short (approx 8 hrs)	Several Days
Hypotension in humans	No	Yes
GI effects in humans	No	Yes

VMAT = Vesicular Monoamine Transporter
Type 1 and 2, coded by two distinct genes, 8p21.3 and 10q25

Table 2. Patient Demographics

	HD	Chorea	*p*
Male (Female)	27 (41)	14 (16)	ns
Age at symptom onset in years			
Mean	48.7	39.1	< 0.03
SE	1.4	5.3	
Range	15.6 – 77.8	0.0 – 78.4	
Duration of Symptoms in years			
Mean	7.2	6.7	ns
SE	0.6	1.7	
Range	0.0 – 23.5	0.1 – 37.2	
Age at initial TBZ treatment in years			
Mean	55.6	45.8	< 0.02
SE	1.4	5.3	
Range	31.7 – 78.7	3.0 – 80.2	
Duration of TBZ treatment in months			
Mean	27.8	17.6	ns
SE	3.1	5.6	
Range	0.2 – 101.0	0.7 – 132.6	

Results

During period of January 1997 and January 2004, a total of 98 patients, 68 with HD and 30 with other forms of chorea, received TBZ for the treatment of chorea with a mean duration of 24.7 ± 26.2 months (range: 0.2 – 132.6). The mean age at symptom onset was 45.7 ± 19.3 years (range: 0.0 – 78.4) and the mean age at initial TBZ treatment was 52.6 ± 19.2 years (range: 3.0 – 80.2). Patients reached an initial stable mean dose at 50.6 ± 29.3 mg of TBZ per day and were maintained at 64.1 ± 38.7 mg per day as their last stable dose.

Differences by disease category were found among some demographic characteristics and illness severity with age at symptom onset and age at initial TBZ treatment both occurring later among patients with HD than patients with some other form of chorea. [Table 2] Analysis of baseline severity of chorea shows that those patients requiring treatment with tetrabenazine had at least moderate to severe chorea. [Table 3]

As of January 2004, 63.6% (HD = 61.8%; chorea = 66.7%) of patients were still being treated with TBZ, 25.5% (HD = 26.5%; chorea = 23.3%) were withdrawn from treatment, and no post-drug follow-up were available in 11.2% (HD = 11.8%; chorea = 6.7%) of patients.

Response rate did not vary over time. [Figure 2] The percentage of patients presenting with an efficacy rating of 1 or 2 is virtually identical at the first (HD = 85.7%; chorea = 81.5%) and at last visit (HD = 88.1%; chorea = 74.1%). For some patients, last visit occurred many years after treatment initiation. [Table 4] Of the 38 patients in whom TBZ therapy was temporarily suspended to determine whether the patient's underlying chorea had spontaneously improved, 81.6% experienced rebound worsening, $\chi^2 = 0.18$, $p < 0.008$.

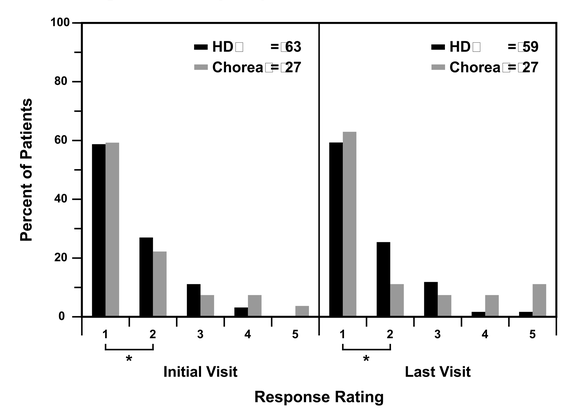
In most cases, patients were treated with 50 – 75 mg of TBZ per day. Less than 20% of patients required doses greater than 75 mg per day. [Table 5] The most frequently reported adverse events were drowsiness and depression, followed by akathisia. [Table 6]

Of the varied reasons for treatment discontinuation among patients with HD, travel/financial difficulties (38.1%) and adverse event intolerability (33.3%) were predominant.

Table 3. Disease Severity

		Baseline Severity (Prior to TBZ Treatment)			
Indication	N	Mild	Moderate	Severe	Disabling
HD	68	0	25	33	10
Chorea	30	0	15	13	2

Figure 2. Efficacy Response at Initial and Last Visit



*1 = marked reduction in abnormal movements, excellent improvement in function
*2 = moderate reduction in abnormal movements, very good improvement in function

Key References

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*Table 4. Duration of TBZ Treatment (N = 89) **

Treatment Duration (yr)	N	%
< 1	40	44.9
1	14	15.7
2	12	13.5
3	6	6.7
4	9	10.1
5	3	3.4
6	1	1.1
7	2	2.2
8	1	1.1
11	1	1.1

* Duration of TBZ treatment for 9 patients could not be determined due to unavailable data.

Table 5. TBZ Stable Dosing

	Initial Stable Dose		Last Stable Dose	
Indication	Mean (SD)	Range	Mean (SD)	Range
HD	50.4 (32.1)	12.5 – 200	70.0 (41.7)	25.0 – 300
Chorea	51.0 (22.1)	18.75 – 100	50.9 (27.3)	12.5 – 125

Table 6. Adverse Event (Number Reported)

Adverse Event	HD	Chorea
Drowsiness/fatigue	13	14
Depression	6	2
Nausea/vomiting	3	1
Insomnia	3	3
Akathisia	5	1
Nervousness/anxiety	3	2
Parkinsonism	3	6
Salivation	3	2
Dizziness	3	0
Orthostasis	0	0
Other AEs	10	8

Conclusion

The analysis of a cohort of patients with moderate to severe chorea treated at Baylor College of Medicine with TBZ (25 to 200 mg per day) between January 1997 and January 2004 shows that the drug is effective in the treatment of chorea due to HD and other causes. In 82% of patients the chorea was completely abolished or markedly reduced. In nearly all patients in whom TBZ was discontinued, the chorea deteriorated and again improved when TBZ was reinstated. The high response rate is sustained over the duration of treatment, which for some patients was several years.

Poster designed by Kevin Dat Vuong, MA