Long-Term Tolerability of Tetrabenazine in the Treatment of Hyperkinetic Movement Disorders

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Abstract

OBJECTIVE: To review long-term tolerability of tetrabenazine (TBZ) in the treatment of a variety of hyperkinetic movement disorders. 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 benzoquinolizine 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, Huntington disease (HD), Tourette syndrome (TS), dystonia, and other involuntary movement disorders, but the drug has not yet been approved for the treatment of these disorders in the US. Marked improvement without serious adverse events, was reported in patients treated between 1980 and 1995 at the Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine (Jankovic and Beach, Neurology 48:358-362,1997). We have analyzed our longitudinal data regarding adverse events (AEs) in additional patients treated since 1997. METHODS: A retrospective chart review was performed on subjects treated with TBZ between 1/1997 and 1/2004. Efficacy of TBZ 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 severity and relationship to the study drug. RESULTS: Since 1997, 448 patients (42% male) were treated with TBZ for a variety of movement disorders, including TD (n = 149), dystonia (n = 132), chorea (n = 98), tics (n = 92), and myoclonus (n = 19). The mean age at onset of the movement disorder was 43.0 ± 24.2 years (range: 0.0–82.9) with TBZ starting at a mean age of 50.0 ± 22.3 years (range: 3.0–87.6). Patients remained on treatment for a mean of 2.3 ± 3.4 years (range: 0.0–21.6) and were maintained on 60.4 ± 35.7 mg per day at last visit. As of 1/2004, a majority of patients with either TD (60.4%) or chorea (63.3%) remained on TBZ treatment (p<0.0001). Efficacy response rating of 1 or 2 was virtually identical at the first and at last visit (TD = 83.5%, 85.7%; dystonia = 67.2%, 69.5%; chorea = 84.4%, 81.4%; tics = 76.7%, 77.8%; myoclonus = 76.5%, 71.4%). A subset (n = 132, 69.5%) of patients experienced rebound worsening when TBZ was temporarily discontinued (χ^2 = 0.12, p<0.0001). TBZ was generally well tolerated, but some experienced drowsiness (25%), parkinsonism (15.4%), depression (7.6%), akathi-sia (7.6%), and other less frequent, dose-related side effects. Older age at onset of TBZ treatment and longer duration of TBZ treatment were predictable of parkinsonism as an AE, while the presence of stereotypy was associated with reduced probability of depression as an AE. Of the entire sample, treatment was discontinued in 34.6% of patients and was attri-buted to AE intolerability (17.0%), lack of efficacy (8.5%), and travel/financial difficulties (7.6%). CONCLUSION: TBZ is a safe and effective drug for chronic treatment of hyper-kinetic movement disorders. No serious adverse events occurred, even after more than decades of treatment.

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

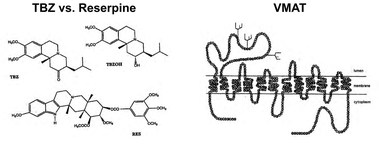


Table 1. Tetrabenazine Versus Reserpine

Pharmacological Properties	Tetrabenazine	Reserpine
Mechanism of Action	Selectively binds hVMAT2 (CNS) Reversibly binds VMAT2 Binds intravesicular site	Binds hVMAT1 (PNS) & hVMAT2 (CNS) Irreversibly binds VMAT 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
VMAT1 and VMAT2 are coded by two distinct genes, 8p21.3 and 10q25, respectively

Introduction

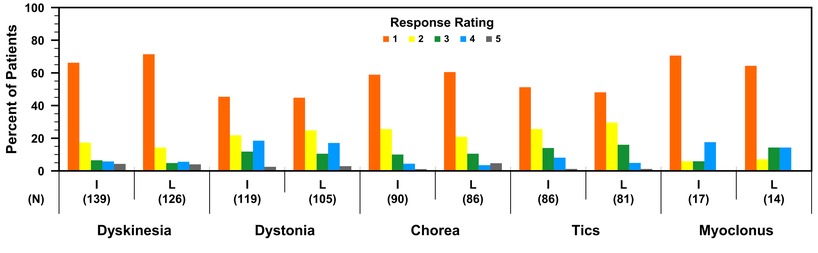
Tetrabenazine (TBZ) is a synthetic benzo-quinolizine that acts as a monoamine-depleting drug by inhibiting central vesicular monoamine transporter type 2 (VMAT2) [Figure 1 and Table 1]. Human VMAT2 is a product of a gene on chromosome 10q25; VMAT1 gene is localized on chromosome 8p21.3. In contrast to VMAT1, which is predominantly expressed in the periphery, VMAT2 is expressed in the brain. The high selectivity of TBZ for VMAT2 (by a factor of 104 over VMAT1) may explain the CNS-specific 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).

Methods

All patients included in this study had involuntary movements that were troublesome or disabling despite optimal 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 1–5 response rating (1 = marked reduction in abnormal movements, excellent improvement in function; 2 = moderate reduction in abnormal movements, very good improvement in function; 3 = moderate improvement in abnormal movements, only mild or no improvement in function; 4 = poor or no response; 5 = worsening) (Jankovic J, Beach J. Neurology 1997;48:358-362). Adverse events (AEs) 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 AE the investigator assigned a level of relationship to TBZ as either probable, possible, or unlikely. In addition, AEs 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 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.

Figure 2. Efficacy Response at Initial and Last Visit per Indication of TBZ Treatment



I = Initial Visit
L = Last Visit

1 = Marked reduction in abnormal movements, excellent improvement in function
2 = Moderate reduction in abnormal movements, very good improvement in function

Table 2. Demographic Information among Patients with Hyperkinetic Movement Disorders Receiving Tetrabenazine Treatment

	Hyperkinetic Movement Disorder											
	Dyskinesia			Dystonia			Chorea			Tics			Myoclonus		
N	149			132			98			92			19		
	Mean (SE)	Range		Mean (SE)	Range		Mean (SE)	Range		Mean (SE)	Range		Mean (SE)	Range	
Age, years															
Sx onset	59.8 (1.2)	2.8 –	82.7	44.6 (1.8)	0.2 –	78.7	45.7 (2.0)	0.0 –	78.4	12.9 (1.6)	2.0 –	65.8	47.4 (5.3)	1.2 –	82.2
Initial TBZ Tx	65.0 (1.1)	29.2 –	86.4	53.1 (1.7)	5.6 –	87.6	52.6 (1.9)	3.0 –	80.2	24.1 (1.7)	8.2 –	72.2	49.3 (5.3)	4.3 –	82.6
Duration, years															
Initial Sx	5.2 (0.6)	0.0 –	46.4	8.5 (0.9)	0.2 –	57.5	7.0 (0.7)	0.0 –	37.2	11.3 (1.3)	0.1 –	64.3	1.9 (0.5)	0.1 –	7.5
TBZ Tx	2.5 (0.2)	0.0 –	11.3	3.0 (0.4)	0.0 –	21.6	2.1 (0.2)	0.0 –	11.1	1.6 (0.3)	0.0 –	20.4	1.7 (0.8)	0.1 –	9.0

TBZ = Tetrabenazine; Sx = Symptom; Tx = Treatment

Results

During period of January 1997 and January 2004, a total of 448 patients (42% male), received TBZ for the treatment of hyperkinetic movement disorders including tardive dyskinesia (TD), Huntington disease (HD) and other choreas, Tourette syndrome (TS) and other tics, dystonia and myoclonus [Table 2]. Majority of patients had at least moderate to severe movement disorder [Table 3]. With the exception of a greater proportion of males to females with tics (χ^2 = 0.11, p<0.0001) and greater proportion of females to males with TD (χ^2 = 0.08, p<0.0001) there was relatively equal gender distribution across the five hyperkinetic movement disorder categories. The mean age at onset of the movement disorder was 43.0 ± 24.2 years (range: 0.0–82.9). TBZ was started at a mean age of 50.0 ± 22.3 (range: 3.0–87.6) and the treatment was maintained for a mean of 2.3 ± 3.4 years (range: 0.0–21.6). At the last visit, the mean daily dose was 60.4 ± 35.7 mg. 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. As of 1/2004, a majority of patients with either TD (60.4%) or chorea (63.3%) remained on TBZ treatment (p<0.0001); a smaller proportion of patients with dystonia, tics, and myoclonus continued treatment with TBZ [Table 4].

Follow-up data was available on 78.9 to 92.4% of all patients initiated on TBZ; one patient has been followed for 21 years [Table 5]. Response rate did not vary over time across the five hyperkinetic movement disorders [Figure 2]. The percentage of patients presenting with a response rating of 1 or 2 was virtually identical at the first and at last visit (TD = 83.5%, 85.7%; dystonia = 67.2%, 69.5%; chorea = 84.4%, 81.4%; tics = 76.7%, 77.8%; myoclonus = 76.5%, 71.4%). Of the 190 patients in whom TBZ therapy was temporarily suspended to determine whether the patient's underlying hyperkinetic movement disorder had spontaneously improved, 69.5% experienced rebound worsening (χ^2 = 0.12, p<0.0001).

The most frequently reported AEs were drowsiness and parkinsonism, followed by depression and akathisia [Table 6]. The reported frequency of AEs is artificially high because we usually increase the dosage of TBZ until there is a desirable improvement in the underlying movement disorder or patients experienced AEs. Based on sequential logistic regression analysis, older age at initiation of TBZ (odds ratio = 1.06, 1.03–1.09 $CI_{95\%}$, p<0.0001) and longer duration of TBZ treatment (odds ratio = 1.12, 1.04–1.20 $CI_{95\%}$, p<0.003) were predictable of parkinsonism as an AE, while the presence of stereotypy (odds ratio = 0.04, 0.00–0.34 $CI_{95\%}$, p<0.0035) reliably reduced the probability of depression as an AE. All AEs were dose related and abated when dosage was reduced. In some cases, the patients were willing to tolerate the AEs, including parkinsonism and akathisia, or obtained symptomatic relief from amantadine, dopamine agonists or levodopa (parkinsonism) or pro-pranolol (akathisia), respectively, and continued TBZ treatment. Of the varied reasons for treatment discontinuation in 34.6% patients with hyperkinetic movement disorders, AE intolerability (17.0%), lack of efficacy (8.5%), and travel/financial difficulties (7.6%) were predominant.

Table 3. Disease Severity by Indication

		Baseline Severity (Prior to TBZ Treatment)			
Indication	N	Mild	Moderate	Severe	Disabling
Dyskinesia	149	1.3	40.3	50.3	8.1
Dystonia	132	0.0	37.4	45.8	16.8
Chorea	98	0.0	40.8	46.9	12.2
Tics	92	1.1	47.8	46.7	4.3
Myoclonus	19	5.3	52.6	26.3	15.8

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Conclusion

The analysis of a cohort of patients with moderate to severe involuntary movements 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 hyperkinetic movement disorders of varied etiology. In most patients in whom TBZ was discontinued, the involuntary movement returned and again improved when TBZ was reinstated. Drowsiness, parkinsonism, depression and akathisia were the most common side effects, but these symptoms improved with reduction in dosage. There was no evidence of TD. The high response rate is sustained over the duration of treatment, which for some patients was more than two decades.

Table 4. TBZ Treatment Disposition by Indication

		TBZ Treatment Disposition, %		
Indication	N	Ongoing	Withdrawn	No FU
Dyskinesia	149	60.4 *	30.2	9.4
Dystonia	132	43.9	40.2	15.9
Chorea	98	63.3 *	25.5	11.2
Tics	92	48.9	41.3	9.8
Myoclonus	19	52.6	26.3	21.1

* p < 0.0001

Table 5. Duration (Years) of TBZ Treatment by Indication

		Hyperkinetic Movement Disorder, % *				
Duration	N	Dyskinesia 136	Dystonia 115	Chorea 89	Tics 85	Myoclonus 15
< 0.5		33.1	40.9	27.0	50.6	66.7
> 0.5		12.5	15.7	18.0	17.6	13.3
1		14.0	7.8	16.9	12.9	0.0
2		12.5	7.8	12.4	5.9	0.0
3		5.9	5.2	6.7	5.9	0.0
4		3.7	3.5	10.1	0.0	0.0
5		5.9	1.7	3.4	0.0	0.0
6		2.9	2.6	1.1	1.2	6.7
7		2.2	1.7	2.2	0.0	0.0
8		0.0	2.6	1.1	2.4	6.7
9		2.9	0.9	0.0	0.0	6.7
10		3.7	1.7	0.0	1.2	
11		0.7	0.9	1.1	0.0	
12			1.7		1.2	
13			0.9		0.0	
14			1.7		0.0	
15			0.0		0.0	
16			0.0		0.0	
17			0.9		0.0	
18			0.0		0.0	
19			0.0		0.0	
20			0.0		1.2	
21			1.7			
FU Data*		91.2%	87.1%	90.8%	92.4%	78.9%

Table 6. Adverse Event Profile Among Patients with Hyperkinetic Movement Disorders Receiving TBZ Treatment

	# of Adverse Event (N = 441)		# of Patients (N = 448)	
Adverse Event [a]	n	%	n	%
Drowsiness	114	25.9	112	25.0
Parkinsonism	71	16.1	69	15.4
Depression	35	7.9	34	7.6
Akathisia	34	7.7	34	7.6
Nausea/Vomiting	26	5.9	25	5.6
Nervousness/Anxiety	23	5.2	23	5.1
Insomnia	22	5.0	22	4.9
Salivation	12	2.7	12	2.7
Dizziness	11	2.5	11	2.5
None reported	—	—	207	46.2

[a] Incidence of reported adverse event ≥ 2.5%

Table 7. Comparison of Adverse Effects Profile by Tetrabenazine Treatment Indication and Disposition

	TBZ Treatment Disposition by Hyperkinetic Movement Disorder, %									
	Dyskinesia		Dystonia		Chorea		Tics		Myoclonus	
Adverse Event	Rx	Wd	Rx	Wd	Rx	Wd	Rx	Wd	Rx	Wd
Total N	90	45	58	53	62	25	45	38	10	5
Drowsiness	27.8	24.4	24.1	20.8	29.0	32.0	44.4 ^	26.3	50.0	20.0
Parkinsonism	36.7 #	17.8	29.3 #	13.2	9.7	8.0	6.7	0.0	10.0	0.0
Depression	1.1	6.7 ^	8.6	15.1	4.8	20.0 #	11.1	5.3	0.0	0.0
Akathisia	8.9	15.6	12.1	9.4	8.1	4.0	6.7	5.3	20.0	0.0
Nausea/Vomiting	3.3	8.9	10.3	5.7	1.6	12.0 #	11.1	7.9	10.0	0.0
Nervousness/Anxiety	7.8	4.4	3.4	3.8	6.5	4.0	2.2	5.3	0.0	0.0
Insomnia	2.2	6.7	1.7	11.3 #	4.8	12.0	6.7	5.3	0.0	0.0
Salivation	2.2	2.2	1.7	1.9	4.8	8.0	2.2	0.0	0.0	0.0
Dizziness	0.0	6.7 #	1.7	3.8	1.6	8.0	0.0	0.0	10.0	0.0
None reported	37.8	28.9	36.2	45.3	50.0	44.0	35.6	39.5	30.0	60.0

Rx = Ongoing; Wd = Withdrawn; ^ p < 0.10; # p < 0.05