Tetrabenazine: Effective Treatment for Tardive Dyskinesia

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Abstract

OBJECTIVE: To describe long-term experience with tetrabenazine (TBZ) in the treatment of tardive dyskinesias. BACKGROUND: Dopamine receptor blocking drugs, commonly used in the treatment of involuntary movements, may cause potentially serious adverse effects, including tardive dyskinesia (TD). This potential serious side effect of dopamine-receptor blocking drugs (neuroleptics) 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, Tourette syndrome, and other involuntary movement disorders, but the drug has not yet been approved for the treatment of these disorders in the US. Marked improvement in chorea was reported in 83% of the first 90 patients, treated between 1980 and 1995 (Jankovic and Beach, Neurology 48:358-362,1997). The drug was well tolerated and no serious adverse events were noted. METHODS: A retrospective chart review was performed on subjects treated with TBZ between 12/1996 and 1/2004. Response to treatment was assessed by a previously published response scale (1 = marked improvement; 4 = no response; 5 = worsening) (Jankovic and Beach, 1997). All adverse events were captured and coded according to their relationship to the study drug. RESULTS: A total of 448 patients were treated with TBZ during the specified period. 149 (115 female) had a diagnosis of TD, mean age of 59.8 (2.8–82.7) years and mean duration of symptoms at initiation of therapy was 5.2 (0–46.4) years. Patients were followed for a mean of 29.7 (0–135.5) months. Severity rating moderate to severe. The mean total daily dose was 56.6 mg (6.25 mg to 200 mg). The most common side effects included parkinsonism (27.5%), drowsiness or fatigue (24.2%), akathisia (10.1%), nervousness/anxiety (6.0%) and nausea (4.6%). 40.9% reported no adverse effects. Most side effects were controlled with dose maintenance or dose-reduction. Of the 139 patients with adequate follow-up, 83.5% reported marked or moderate reduction in abnormal movements (response score of 1 or 2) at first follow-up visit and 85.7% at the last visit (NS by Wilcoxon test). A wide range of concomitant medications were also utilized by these patients, with no apparent drug-drug interaction noted. CONCLUSION: TBZ is a safe and effective drug for the treatment of involuntary movements associated with TD. The benefits are sustained for years.

Background

Tetrabenazine (TBZ) is a synthetic benzoquinolizine 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.

Methods

Patients were included if they met the following criteria: the presence of troublesome or disabling involuntary movements; willing and able to give informed consent; willing to perform videotape protocol before and after treatment, and have adequate follow-up every three to six months per protocol.

Response to treatment was assessed using a 1 to 5 response rating scale (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), previously reported in Jankovic J, Beach J. Neurology 1997. Adverse events (AE) were captured, as well as specific questions related to level of alertness, mood and motor function. The patients were also examined for any evidence of parkinsonism. AE's were assessed for causality by the investigator and assigned a level of relationship to TBZ as either "probable", "possible", or "unlikely".

Figure 1.

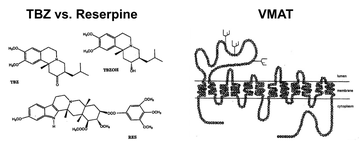


Table 1. Tetrabenazine Versus Reserpine

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
VMAT1 and VMAT2 are coded by two distinct genes, 8p21.3 and 10q25, respectively

Results

In most cases, patients were treated with 50-75 mg of TBZ per day; less than 13.7% of patients required doses greater than 75 mg per day. The reported frequency of AE's is artificially high because we usually increase the dosage of TBZ until there is a desirable improvement in the underlying movement disorder or patients experience an AE. All AE's were dose related and abated when dosage was reduced or discontinued. In some cases, patients were willing to tolerate the AE, including parkinsonism and akathisia. Others obtained symptomatic relief from amantadine, dopamine agonists or levodopa (parkinsonism) or propranolol (akathisia), and continued TBZ treatment.

Table 2. Demographic Characteristics Among Patients with Tardive Dyskinesia Receiving Tetrabenazine Treatment

	Total	Male	Female	p
Patients, N	149	34	115	< 0.0001
Age at Sx onset, years				
Mean ± SE	59.8 ± 1.2	54.2 ± 3.2	61.4 ± 1.2	< 0.02
Range	2.8 – 82.7	2.8 – 76.8	19.2 – 82.7	
Duration of Sx, years				
Mean ± SE	5.2 ± 0.6	6.8 ± 1.7	4.7 ± 0.5	ns
Range	0.0 – 46.4	0.2 – 46.4	0.0 – 25.9	
Age at initial TBZ Tx, years				
Mean ± SE	65.0 ± 1.1	61.0 ± 2.3	66.1 ± 1.2	< 0.05
Range	29.2 – 86.4	29.2 – 79.3	31.3 – 86.4	
Duration of TBZ Tx, years				
Mean ± SE	2.5 ± 0.2	2.0 ± 0.4	2.6 ± 0.3	ns
Range	0.0 – 20.4	0.0 – 20.4	0.0 – 8.0	

TBZ = Tetrabenazine; Sx = Symptom; Tx = Treatment

Figure 2. Baseline Tardive Dyskinesia Severity (N = 149)

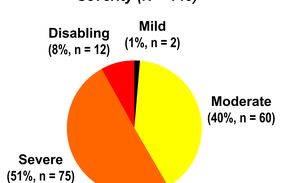


Figure 3. TBZ Stable Dosing

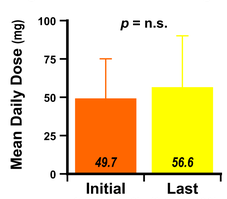
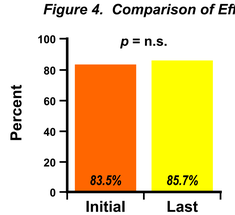


Figure 4. Comparison of Efficacy Response at Initial and Last Visit ^



^ Percent of patients with response rating of 1* and 2*

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

Figure 5. Adverse Events Related to TBZ Treatment of Tardive Dyskinesia (N = 149)

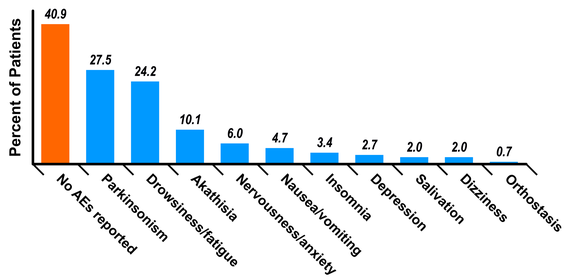


Table 3. Patient Disposition (N = 149)

Disposition	n	(%)
Ongoing (as of 01/04)	90	(60.4)
Withdrawn	45	(30.2)
Lost to follow-up	14	(9.4)

Table 4. Reasons for Treatment Discontinuation (N = 51)

Discontinuation	n	%
Adverse event	23	(45.1)
Travel / Financial	10	(19.6)
Lack of efficacy	6	(11.8)
Better results with BTX	1	(2.0)
Spontaneously improvement	1	(2.0)
Death	0	(0.0)
Other	10	(19.6)

Conclusions

The analysis of a cohort of patients with moderate to severe TD treated at Baylor College of Medicine with TBZ (6.25–200 mg per day) between January 1997 and January 2004 shows that the drug is effective in the treatment of tardive dyskinesia. In most patients in whom TBZ was discontinued, the involuntary movement returned and again improved when TBZ was reinstated. Parkinsonism, drowsiness, akathisia, anxiety and nausea were the most common side effects, but these symptoms improved with reduction in dosage. The high response rate is sustained over the duration of treatment, which for some patients was more than a decade.

Selected References

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