Efficacy and Safety of Tetrabenazine in the Treatment of Tic Disorders

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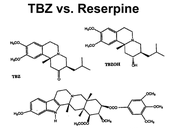
Abstract

OBJECTIVE: To review the long-term efficacy and safety of tetrabenazine (TBZ) in the treatment of tic disorders. BACKGROUND: Dopamine receptor blocking drugs (DRBD), also known as neuroleptics, are commonly used in the treatment of involuntary movements and 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. TBZ has been reported to have an ameliorating effect in a variety of hyperkinetic movement disorders, including TD, Tourette syndrome (TS), Huntington disease, dystonia, and other involuntary movement disorders, but the drug has not yet been approved for the treatment of these disorders in the US. Jankovic and Beach (1997) reported marked improvement without serious adverse events in patients treated between 1980 and 1995 at the Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine. 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 January, 1997 and January, 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, 92 (20.5%) of 448 patients received TBZ for the treatment of tics. The mean age at onset of tics was 12.9 years (range: 2.0–65.8) with TBZ starting at a mean age of 24.1 years (range: 8.2–72.2). Patients remained on treatment for a mean of 1.6 years (up to 20.4 years) and were maintained on 53.3 mg per day (range: 6.25–150) at last visit. Efficacy response rating of 1 or 2 was virtually identical at the first and at last visit (76.7% and 77.8%, respectively). A subset (n = 18, 50.0%) of patients experienced rebound worsening when TBZ was temporarily discontinued. TBZ was generally well tolerated, though some experienced drowsiness (32.6%), nausea/vomiting (8.7%), depression (7.6%), insomnia (6.5%), akathisia (5.4%), and other less frequent, dose-related side effects. Longer duration of treatment and older age at onset of tics (within the first two years of treatment) were predictive of improved efficacy. Treatment was discontinued in 41.3% of patients and was attributed to AE intolerability (21.7%), lack of efficacy (10.9%), and travel/financial difficulties (7.6%). CONCLUSION: TBZ is a safe and effective drug for chronic treatment of hyperkinetic movement disorders such as Tourette syndrome and other tic disorders. No serious AEs occurred, even after more than a decade of treatment.

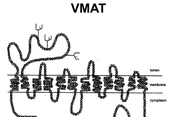
Introduction

Figure 1.

TBZ vs. Reserpine



VMAT



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 gene is found 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.

TBZ was first introduced in 1960 as an antipsychotic drug. While the drug never gained wide usage as a tranquilizer, it has been found beneficial in some hyperkinetic movement disorders. In the absence of any documented case of tardive dyskinesia as an adverse effect of treatment, TBZ continues to have a distinct advantage over other DRBD commonly used in the treatment of hyperkinetic movement disorders.

Over a thousand patients with 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

Study inclusion was based on all patients with some form of tic disorder whose involuntary movements were disabling or interfering with social, academic, or occupational activities 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. TBZ was dispensed and dose titration schedule given for each subject. Patients were followed every three to six months, at which time treatment efficacy was assessed using a 1–5 response rating (Jankovic J, Beach J. Neurology 1997;48:358-362). AEs were captured by an open-ended question ("have you noted any new symptoms since your last visit?"). This was followed by specific questions related to level of alertness, mood and motor function. 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 entered into a database. The completeness and accuracy of the entered data was verified by an independent audit of approximately 25% of the records.

All patients who began therapy during the period of January 1997 through January 2004 were included in this retrospective study. Patients who began therapy prior to December 1996 and were still on therapy after 1997 were also included.

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

Table 2. Demographic Characteristics Among Patients with Tics Receiving Tetrabenazine Treatment

	Total	Male	Female	*p*
Patients, N	92	68	24	< 0.0001
Age at Sx onset, years				
Mean ± SE	12.9 ± 1.6	10.5 ± 1.5	19.4 ± 4.0	< 0.01
Range	2.0–65.8	2.4–55.6	2.0–65.8	
Duration of Sx, years				
Mean ± SE	11.3 ± 1.3	9.8 ± 1.2	15.6 ± 3.3	< 0.05
Range	0.1–64.3	0.8–64.3	0.1–57.5	
Age at initial TBZ Tx, years				
Mean ± SE	24.1 ± 1.7	20.2 ± 1.7	35.0 ± 4.0	< 0.0001
Range	8.2–72.2	8.2–70.4	10.6–72.2	
Duration of TBZ Tx, years				
Mean ± SE	1.6 ± 0.3	1.8 ± 0.4	1.0 ± 0.4	ns
Range	0.0–20.4	0.0–20.4	0.0–8.0	

TBZ = Tetrabenazine; Sx = Symptom; Tx = Treatment

Results

During period of January 1997 and January 2004, 92 (20.5%) of 448 patients received TBZ for the treatment of TS and other tics. The remaining patients were treated for other hyperkinetic movement disorders included TD, HD and other choreas, dystonia and myoclonus.

[Table 2] Mean age at onset of tics was 12.9 years (SE = 1.6; range: 2.0–65.8).

TBZ was started at a mean age of 24.1 years (SE = 1.7; range: 8.2–72.2).

Treatment was maintained for a mean of 1.6 years (SE = 0.3; range: 0.0–20.4).

Greater proportion of males to females with tics ($\chi^2 = 21.0$, $p < 0.0001$)

[Figure 2] Majority of patients had at least moderate to severe tic disorder; 48.9% remained on TBZ treatment.

[Figure 3] Efficacy of response did not vary over time (Wilcoxon signed rank test, $p = 0.99$).

The percentage of patients presenting with a response rating of 1 or 2 was virtually identical at the first and at last visit (76.7% and 77.8%, respectively).

[Table 3] Most frequently reported AEs were drowsiness and nausea/vomiting, followed by depression, insomnia, and akathisia.

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.

At the last visit, the mean daily dose was 53.3 mg (SD = 29.3; range: 6.25–150). Upon temporary suspension of TBZ therapy, 50.0% of 36 patients experienced rebound worsening ($\chi^2 = 0.0$, $p = 1.0$).

Of the varied reasons for treatment discontinuation in 41.3% of 92 patients, AE intolerability (21.7%), lack of efficacy (10.9%), and travel/financial difficulties (7.6%) were predominant. Better results with botulinum toxin injections were reported in 2.2% of patients.

Figure 2. Disease Severity by TBZ Treatment Disposition (N = 92)

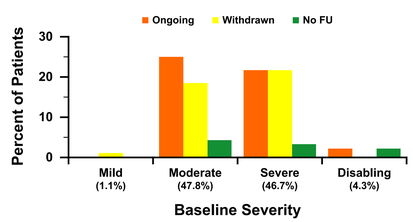
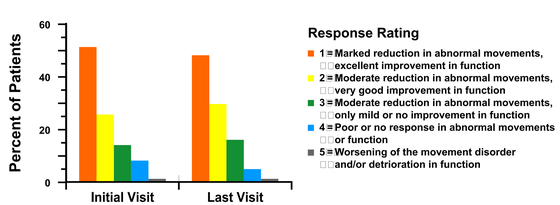


Figure 3. Efficacy Response of TBZ Treatment at Initial and Last Visit



Conclusions

The analysis of a cohort of patients with tic disorder whose moderate to severe involuntary movements were treated at Baylor College of Medicine with TBZ (6.25 to 150 mg per day) between January 1997 and January 2004 shows that TBZ is an effective treatment in the moderate to marked reduction in abnormal movements that resulting in very good to excellent improvement in function. The high response rate is sustained over the duration of treatment, which for some patients was more than a decade.

In half of patients in whom TBZ was discontinued, the involuntary movement returned and again improved when TBZ was reinstated.

Drowsiness, nausea/vomiting, depression, insomnia and akathisia were the most common side effects, but these symptoms improved with reduction in dosage. There was no evidence of TD.

This population of patients also utilized a wide variety of concomitant medications with no apparent drug-drug interaction noted.

Overall TBZ is safe and well tolerated in this population and has the distinct advantage over the traditional DRBD often used in the treatment of this disorder.

Table 3. Comparison of Adverse Effects Profile by TBZ Treatment Disposition

		TBZ Treatment Disposition, %	
		Ongoing	Withdrawn
Adverse Event	n	45	38
Drowsiness	30	44.4 ^	26.3
Nausea/Vomiting	8	11.1	7.9
Depression	7	11.1	5.3
Insomnia	6	6.7	5.3
Akathisia	5	6.7	5.3
Nervousness/Anxiety	4	2.2	5.3
Parkinsonism	3	6.7	0.0
Salivation	1	2.2	0.0
None reported		35.6	39.5

^ $p < 0.10$

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