Safety and Efficacy of Tetrabenazine in Childhood Hyperkinetic Movement Disorders

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Abstract

OBJECTIVE: To evaluate the safety and efficacy of tetrabenazine (TBZ) in childhood hyperkinetic movement disorders. BACKGROUND: TBZ is a synthetic benzoquinolizine that acts as a central monoamine-depleting drug by inhibiting central vesicular monoamine transporter type 2 (VMAT2). TBZ has been previously reported to be effective in the treatment of hyperkinetic movement disorders such as Huntington's disease and tardive dyskinesia with a marked reduction in the associated hyperkinesia. METHODS: All subjects have been evaluated and followed in the Movement Disorders Clinic at Baylor College of Medicine. A retrospective chart review was performed on subjects treated with TBZ from 12/96 through 1/2004. Response to treatment was measured using a 1-5 scale and diagnostic severity was rated using a 1-4 scale both previously reported by Jankovic and Beach [Neurology 1997;48:358 -362]. RESULTS: A total of 448 subjects were treated with TBZ during the specified period and 76 (52 male) were under the age of 18 (mean age 12.4 ears, range: 3.0 -17.9) at the initiation of treatment. The indication for treatment were as follows: tics n = 53 (69.7%); dystonia n = 12 (15.7%); chorea n = 10 (13.2%) and myoclonus n = 3 (3.9%). The patients had symptoms for a mean of 5.9 years duration of symptoms at initiation of therapy and they were followed for 18.7 months. The mean total daily dose was 49.3 mg (6.25-150 mg). Improvement associated with TBZ therapy was most robust in myoclonus (100%), chorea (89%); and tics (72%) compared to dystonia with only (50%) at last evaluation. The most common side effects included drowsiness or fatigue (35.5%), nausea (10.5%), depression (9.2%), akathisia (6.5%) and insomnia (3.9%). No parkinsonism was seen in this population. 36.8% of the subjects reported no adverse effects. Most side effects were controlled with dose maintenance or dosereduction. Wilcoxon analysis showed no significant decline in efficacy from initial treatment to last evaluation. A wide range of concomitant medications were also utilized by these patients, with no apparent drugdrug interaction noted. CONCLUSION: TBZ is safe and effective for the treatment of hyperkinetic movement disorders in a pediatric population.

Introduction

Tetrabenazine (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 and Results

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 [Table 1]. 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. Efficacy Rating of Tetrabenazine Treatment

Response Rating	Abnormal Movements	Function
1	Marked reduction	Excellent improvement
2	Moderate reduction	Very good improvement
3	Moderate reduction	Only mild or no improvement
4	Poor or no response	Poor or no response
5	Worsening	Detrioration

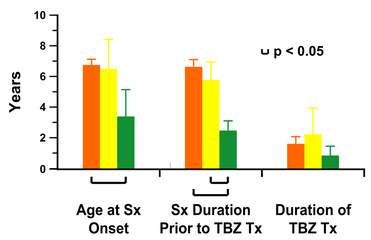
Jankovic J, Beach J. Neurology 1997;48:358-362

Table 2. Sex Distribution (%)

Indication	N	Total	Male	Female	*p*
Tics	53	69.7	83.6	33.3	< 0.0001
Dystonia	12	15.8	9.1	33.3	< 0.02
Chorea	10	13.2	7.3	28.6	< 0.03
Total ^	76	—	72.4	27.6	< 0.0001

^ Includes myoclonus (n = 3)

Figure 1. Demographic Information (Mean ± SE)

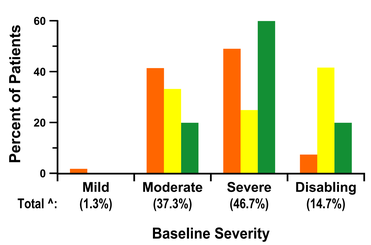


Patients with chorea had a younger age of Sx onset than did patients with tics, $p < 0.05$.

Sx duration prior to TBZ Tx was shortest among patients with chorea than patients with either tics or dystonia, $p < 0.05$.

^N = 76

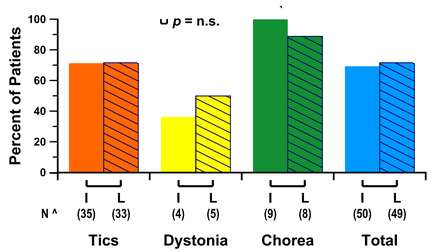
Figure 2. Disease Severity at Baseline



Majority of pediatric patients had at least moderate to severe hyperkinetic movement disorder.

^N = 76

Figure 3. Efficacy Response of TBZ Treatment at Initial (I) and Last (L) Visit



Excellent to marked reduction in abnormal movements with moderate to excellent improvement in function was maintained within each indication as well as among the entire group of pediatric patients, p = n.s.

^ Number of patients with response rating of 1* or 2* [Table 1]

Table 3. Tetrabenazine Stable Dosing ^

	Initial Stable Dose		Final Stable Dose	
Indication	Mean (SD)	Range	Mean (SD)	Range
Tics	42.1 (23.3)	12.5–100.0	49.1 (26.7)	6.3–150.0
Dystonia	40.6 (27.2)	12.5–100.0	43.8 (32.0)	6.3–125.0
Chorea	46.9 (22.7)	18.8–75.0	50.0 (25.8)	25.0–100.0
Total	43.5 (23.3)	12.5–100.0	50.0 (27.8)	6.3–150.0

^ All within- and between-group comparisons, p = n.s.

Table 4. Patients Reporting an Adverse Event Relating to TBZ Treatment (%)

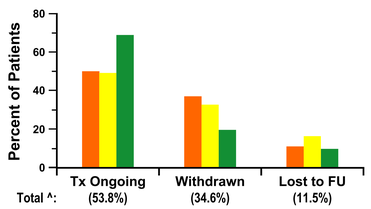
Adverse Event	Tics *n = 53*	Dystonia *n = 12*	Chorea *n = 10*	Total *N = 76*
Drowsiness/fatigue	18 (34.0)	3 (25.0)	5 (50.0)	26 (34.2)
Nausea/vomiting	6 (11.3)	1 (8.3)	0 (0.0)	8 (10.5)
Depression	6 (11.3)	1 (8.3)	0 (0.0)	7 (9.2)
Akathisia	2 (3.8)	1 (8.3)	0 (0.0)	3 (3.9)
Insomnia	3 (5.7)	0 (0.0)	0 (0.0)	3 (3.9)
Nervousness/anxiety	2 (3.8)	1 (8.3)	0 (0.0)	3 (3.9)
Salivation	1 (1.9)	0 (0.0)	1 (10.0)	2 (2.6)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Orthostasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Other AEs	13 (24.5)	2 (16.7)	0 (0.0)	16 (21.1)
None reported	19 (35.8)	3 (25.0)	4 (40.0)	27 (35.5)

Table 5. Reasons for Treatment Discontinuation (%)

Discontinuation	Tics *n = 22*	Dystonia *n = 5*	Chorea *n = 3*	Total *N = 31*
Adverse event	11 (50.0)	4 (80.0)	2 (66.7)	17 (54.8)
Lack of efficacy	6 (27.3)	1 (20.0)	0 (0.0)	7 (22.6)
Administrative ^	11 (4.5)	0 (0.0)	0 (0.0)	2 (6.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	4 (18.2)	0 (0.0)	1 (33.3)	5 (16.1)

^ Includes Travel/Financial reasons. For many patients, traveling back to Baylor is difficult. In addition, some patients cannot afford the cost of tetrabenazine.

Figure 4. Patient Disposition



More than half of all pediatric patients as well as within each indication remained on TBX Tx.

^N = 76

Conclusions

The analysis of all pediatric patients whose moderate to severe involuntary movements were treated at Baylor College of Medicine with tetrabenazine (6.25–150 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. The amount of symptom reduction generally resulted in very good to excellent improvement in functioning. Among each of the pediatric hyperkinetic movement disorders, improved efficacy was sustained over the duration of treatment, which for 20% of patients was between 2 and 10 years.

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

Drowsiness, nausea/vomiting, and depression were the most common side effects, but these symptoms improved with dose reduction. There was no evidence of tardive dyskinesia or parkinsonism.

Overall tetrabenazine is safe and well tolerated in this population with pediatric hyperkinetic movement disorders.

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