Tetrabenazine in the Treatment of Tourette Syndrome

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Abstract

Objective: To evaluate the safety and efficacy of tetrabenazine (TBZ) in patients with tics associated with moderate to severe Tourette syndrome (TS).

Background: TBZ is a synthetic benzoquinolizine compound that has been shown to be a central monoamine-depleting and dopamine-receptor blocking drug. 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.

Design/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 1/01. 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 354 subjects were treated with TBZ during the specified period and 77 had a diagnosis of TS. Of the 77 patients with TS there is a mean of 10 months duration of symptoms at initiation of therapy and 23.7 months duration of follow-up. Gender and age distribution is as follows: 58 are male and 19 are female with a mean age of 14.8 (1.97 - 71.4) years. Subjects reported a moderate (2 or 3 on the above scale) to marked reduction (1 on the scale) in abnormal movements with improvement in overall function. The mean total daily dose is 50.4 mg (6.25 mg to 125 mg) per day. The most common side effects included drowsiness or fatigue (36.4%), nausea (10.4%), depression (9.1%), insomnia (7.8%), and parkinsonism (6.5%). Only 1.2% of subjects reported a worsening of their tics. 22.1% of the subjects reported no adverse effects. Most side effects were controlled with dose maitenance or dose-reduction. The Wilcoxon signed rank exact test (2-tailed) was performed (-3.3;p<0.001) showing statistical significance in the comparison of diagnostic severity at the initial versus the final assessment. A wide range of concomitant medications were also utilized by these patients, with no apparent drug-drug interaction noted.

Conclusion: TBZ has a distinct advantage over the traditional dopamine receptor blocking drugs often used in the treatment of this disorder, especially since it is not associated with tardive dyskinesia.

Background

Movement disorders, particularly the hyperkinesias, are among the most prevalent and the most disabling of neurological disorders. The hyperkinesias are characterized by excessive, involuntary, purposeless and repetitive movements, which may involve the face, limbs, or the entire body. One of the most common forms of hyperkinesias are the orofacial dyskinesias which are usually associated with tardive disorders. Other hyperkinetic disorders include chorea, athetosis, ballism, tics, dystonia, myoclonus, stereotypies and akathisia.

Tetrabenazine, a benzoquinolizine compound that depletes cerebral monoamines and blocks dopamine receptors in rat brain, 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. Tetrabenazine rarely causes an acute dystonic reaction, but no documented case of tardive dyskinesia secondary to tetrabenazine has ever been reported. Therefore, tetrabenazine has a distinct advantage over the other antidopaminergic (neuroleptic) drugs commonly used in the treatment of hyperkinetic movement disorders.

Methods

All patients included in this study were evaluated in the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC), Baylor College of Medicine (BCM), Houston, Texas. Patients were considered candidates for therapy with tetrabenazine (TBZ) if, based on their initial or subsequent evaluations, they had an involuntary movement disorder (chorea, tardive stereotypy, tics, dystonia, myoclonus, ballism, and other hyperkinesias) that was troublesome or interfering with social, academic, or occupational activities. All patients gave written informed consent approved by the BCM Institutional Review Board (IRB) for Tetrabenazine Compassionate Use Protocol. After signing a consent form permitting photographing and videotaping, all patients were videotaped prior to the institution of TBZ therapy. Demographic information was elicited and crosschecked with the patient database of the PDCMDC. A complete history, neurological examination, and review of concomitant medications were performed. The drug was dispensed and dose titration schedule given for each subject. All patients who began therapy during the period of January 1997 through March 2002 were included in this retrospective study. Patients who began therapy prior to December 1996 and were still on therapy after 1997 were also included.

Case report forms (CRFs) were designed to capture all the pertinent data to be extracted and after a thorough review and several revisions it was finalized. To minimize inter-rater variability, two persons performed the retrospective chart review. Only the data manager and one other individual, so as to minimize input error variability, performed all data entries. After data from the first 20 charts were entered the principal investigator (PI), reviewed all the records for quality assurance and to clarify any issues related to extraction of data and standardize interpretation of data that required clinical judgment. Approximately 30% of all charts entered into the database were reviewed by the PI, in an effort to ensure high quality standard of data extraction and data entry. The quality assurance review, completed on March 2002, was highly satisfactory with excellent accuracy of data extraction and data entry.

Results and Discussion

All data analysis was performed with SPSS v10. Demographic information, treatment response, adverse event profile, and reasons for discontinuation from or change during tetrabenazine treatment among patients with Tourette syndrome (TS) are presented in tabular format.

The authors report that in our series of 58 males and 19 females with TS, 83% of those treated with TBZ showed a marked to moderate improvement in their symptoms with 71.3% also reporting an improvement in function. The mean total daily dose is 50 mg (6.25-125 mg). We saw no acute dystonic reactions as previously reported in a small number of patients (2.3%) with TS. The adverse events experienced were as expected, with a higher incidence of drowsiness/fatigue, nausea, depression and insomnia than is seen in the older patients treated with TBZ. This population of patients also utilize 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 antidopaminergic (typical neuroleptic) drugs often used in the treatment of this disorder.

Table 1.
Demographic Information among Patients with Tourette Syndrome Receiving Tetrabenazine Treatment (N = 77)

Demographic information (N = 77, 75% male)	Mean ± SD	Range
Age at initial TBZ treatment (yr)	14.8 ± 17.4	2.0 – 71.4
Initial symptom duration (mo)	10.2 ± 9.7	0.1 – 48.7
TBZ treatment duration (mo)	23.7 ± 41.1	0.1 – 245.3
Dose at last visit (mg/d)	50.4 ± 27.0	6.3 – 125.0

Table 2.
Response to Tetrabenazine Treatment among Patients with Tourette Syndrome (N = 77)

Response rating	Initial response N	Initial response %	Response at last visit N	Response at last visit %
1) Marked reduction in abnormal movements, excellent improvement in function	39	50.6	34	44.2
2) Moderate reduction in abnormal movements, very good improvement in function	19	24.7	21	27.3
3) Moderate reduction in abnormal movements, only mild or no improvement in function	8	10.4	9	11.7
4) Poor or no response in abnormal movements or function	5	6.5	3	3.9
5) Worsening of the movement disorder and/or detrioration in function	0	0.0	0	0.0

Table 3.
Adverse Event Profile among Patients with Tourette Syndrome Receiving Tetrabenazine Treatment

Adverse event	Number of adverse events (N = 84) n	Number of adverse events (N = 84) %	Number of patients (N = 77) n	Number of patients (N = 77) %
Drowsiness	28	33.3	28	36.4
Nausea/vomiting	8	9.5	8	10.4
Depression	8	9.5	7	9.1
Insomnia	6	7.1	6	7.8
Parkinsonism	5	6.0	5	6.5
Nervousness/anxiety	4	4.8	4	5.2
Akathisia	3	3.6	3	3.9
Tremor	2	2.4	2	2.6
"Trance-like/zombie"	2	2.4	2	2.6
Rash	2	2.4	2	2.6
Drooling	2	2.4	2	2.6
Speech difficulties/slurred	2	2.4	2	2.6
Orthostatic hypotension	1	1.2	1	1.3
Balance/gait difficulties	1	1.2	1	1.3
Bradykinesia	1	1.2	1	1.3
Headaches	1	1.2	1	1.3
Paresthesias	1	1.2	1	1.3
Blurred vision	1	1.2	1	1.3
Restlessness, severe	1	1.2	1	1.3
Increased tics	1	1.2	1	1.3
Palpitation/tachycardia	1	1.2	1	1.3
Cushinoid	1	1.2	1	1.3
Rolling eyes	1	1.2	1	1.3
Suicidal ideation	1	1.2	1	1.3
None reported	—	—	17	22.1

Table 4.
Reasons for Change or Discontinuation of Tetrabenazine among Patients with Tourette Syndrome (N = 77)

Reason	Change with ongoing treatment N	Change with ongoing treatment %	Discontinuation of treatment N	Discontinuation of treatment %
Side effects	20	26.0	17	22.1
Lack of efficacy	5	6.5	7	9.1
Movement disorder spontaneously resolved	0	0.0	0	0.0
Death (unrelated to TBZ)	0	0.0	0	0.0
Travel/financial reasons	2	2.6	6	7.8
Better results with botulinum toxin	0	0.0	1	1.3
Miscellaneous	1	1.3	4	5.2

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