Age-Related Tolerability of Tetrabenazine

Christine B. Hunter, RN, Anchi Wang, MD, Kevin Dat Vuong, MA, and Joseph Jankovic, MD

Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas

Abstract

Objective: To evaluate the safety and efficacy of tetrabenazine (TBZ) in the control of hyperkinetic movement disorders and to examine its age-related tolerability.

Background: TBZ is a synthetic benzoquinolizine 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 a variety of hyperkinetic movement disorders (Jankovic J, Beach J, Neurology 1997;48:358-362), but deter-minants of long-term tolerability have not been previously studied.

Design/Methods: A retrospective chart review was performed on subjects treated with TBZ from 12/96 to 1/01 in the Movement Disorders Clinic at Baylor College of Medicine. In addition to response assessments, the safety profile of TBZ was carefully monitored at each visit. The adverse events (AEs) were categorized as possibly related or probably related to treatment with TBZ.

Results: The primary indication for treatment among 354 subjects were chorea (28.1%), tardive dyskinesia (25.2%), tics (24.4%), dystonia (22.3%), and others (38%). The most common side effects were dose-related. Sequential logistic regression analysis based on the Wald statistic was performed separately on each of the AE's listed above as outcome, first on the basis of eight diagnostic and four treatment predictors (Model 1), and then after addition of age at initial TBZ treatment (Model 2). Comparison of log-likelihood ratios for models with and without age showed that age is a reliable predictor of parkinsonism as an AE ($p < 0.0001$), but the addition of age did not improve prediction of the remaining adverse events.

Conclusion: TBZ is safe and well-tolerated in the treatment of hyperkinetic movement disorders. The higher occurrence of parkinsonism associated with TBZ treatment in the older patients suggests that there is an underlying age-related dopamine deficiency that becomes clinically manifested with TBZ.

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, dystonia, tics, myoclonus, stereotypies and akathisia.

Tetrabenazine (TBZ), 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. TBZ rarely causes an acute dystonic reaction, but no documented case of tardive dyskinesia secondary to tetrabenazine has ever been reported. Therefore, TBZ 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 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 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

Demographic information and adverse event profile among patients with hyperkinetic movement disorders receiving TBZ treatment is presented elsewhere. (Tables 1 and 2)

Sequential logistic regression analysis was performed with SPSS v10 to predict the likelihood of experiencing each adverse effect as outcome, first on the basis of eight diagnostic and four treatment predictors (Model 1), and then after addition of age at initial TBZ treatment (Model 2). The diagnostic predictors were the presence or absence of parkinsonism, tremor, dystonia, stereotypy, tics, chorea, myoclonus, and other movement disorders. Treatment predictors included the initial and last stable dosages, severity, and duration of TBZ treatment.

For each of the seven adverse events, the Hosmer and Lemeshow test revealed a good model fit on the basis of the eight diagnostic and four treatment predictors alone, as well as after the addition of age at initial treatment into the model. (Table 3) Comparison of log-likelihood ratios for models with and without age showed that age is a reliable predictor of parkinsonism as an AE, $\chi^2(1) = 18.89$, $p < 0.0001$, but the addition of age did not improve prediction of the remaining adverse events.

Based on the models' predictive classification for each adverse event and the log-likelihood ratio comparisons, both specificity and positive predictive value significantly increased with the addition of age as a predictor of parkinsonism as an AE. To compensate for inflated Type I error rate with 13 predictors, $\alpha = 0.0038$, two-tailed. Longer duration of TBZ treatment (odds ratio = 1.12, 1.04 – 1.20 $CI_{95\%}$, $p < 0.0025$) and older age at initial treatment (odds ratio = 1.06, 1.03 – 1.09 $CI_{95\%}$, $p < 0.0001$) reliably enhanced prediction 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.

The predicted probability of experiencing each adverse event as a sequential logistic regression function of age at initial TBZ treatment with the diagnostic and treatment predictors as covariates is presented. (Figure 1)

Discussion

TBZ is safe and well-tolerated in the treatment of hyperkinetic movement disorders at all ages irrespective of specific diagnostic category. The higher occurrence of parkinsonism associated with TBZ treatment in the older patients suggests that there is an underlying age-related dopamine deficiency that becomes clinically manifested with the use of TBZ. Sedation was present in 25% of all patients regardless of age. Parkinsonism occurred in about 17% of all subjects. The younger subjects (those in the first 2 decades of life) appeared more likely to have insomnia and depression than the older subjects (those above the 5th decade of life) though not statistically significant. Insomnia was present in 5.5% of subjects and depression in 7.9% of all subjects. The majority of adverse events related to TBZ appeared to be dose related and resolved with maintenance or dose reduction. No serious adverse events were encountered. Overall TBZ is safe and well tolerated in this clinically diverse group of subjects.

Table 1.
Demographic Information among Patients with Hyperkinetic Movement Disorders Receiving Tetrabenazine Treatment

Demographic information (N = 354) (42% male:58% female)	Mean ± SD (years)	Range (years)
Age at initial TBZ treatment	50.2 ± 22.4	3.0 – 87.6
Initial symptom duration	7.2 ± 7.9	0.0 – 53.0
TBZ treatment duration	2.4 ± 3.3	0.0 – 21.6

Table 2.
Adverse Event Profile among Patients with Hyperkinetic Movement Disorders Receiving Tetrabenazine Treatment

	Number of adverse events (N = 366)		Number of patients (N = 354)	
Adverse event [a]	n	%	n	%
Drowsiness	91	24.9	89	25.1
Parkinsonism	62	16.9	61	17.2
Depression	29	7.9	28	7.9
Akathisia	24	6.6	24	6.8
Nausea/Vomiting	22	6.0	21	5.9
Nervousness/Anxiety	21	5.7	21	5.9
Insomnia	20	5.5	20	5.6
None reported	—	—	87	24.6

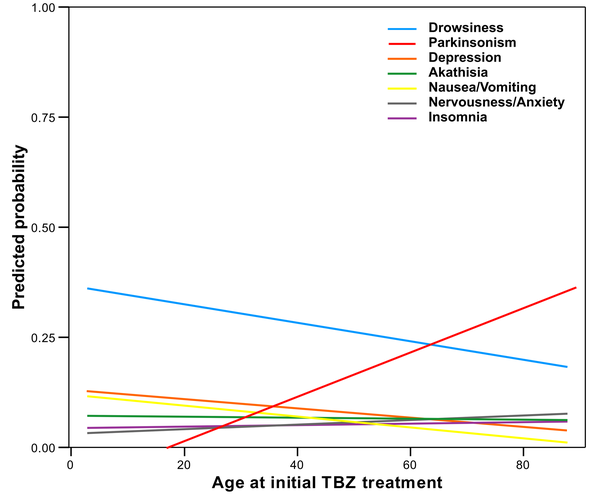
[a] Incidence of reported adverse event ≥ 5%.

Table 3.
Hosmer and Lemeshow Goodness-of-Fit Test by Adverse Event

		Goodness-of-fit		Comparison of log-likelihood ratios
Adverse event	Model	χ^2 ($df = 8$)	p	χ^2 ($df = 1$) p
Drowsiness	1 [a]	8.18	0.42	1.79 0.18
	2 [b]	3.90	0.87	
Parkinsonism	1	3.33	0.91	18.89 < 0.0001
	2	12.95	0.11	
Depression	1	12.75	0.12	0.16 0.69
	2	13.92	0.08	
Akathisia	1	11.96	0.15	1.25 0.26
	2	3.94	0.86	
Nausea/Vomiting	1	3.79	0.88	1.59 0.21
	2	8.02	0.43	
Nervousness/Anxiety	1	3.80	0.88	0.42 0.52
	2	8.48	0.39	
Insomnia	1	3.63	0.89	0.91 0.34
	2	4.22	0.84	

[a] Derived from eight diagnostic and four treatment predictors.
[b] Derived from Model 1 and after addition of age at initial treatment as a predictor.

Figure 1.
Predicted Probability of Experiencing an Adverse Event as a Sequential Logistic Regression Function of Age with Diagnostic and Treatment Predictors as Covariates



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