Tetrabenazine Treatment for Tardive Dyskinesia: Assessment by Randomized Videotape Protocol

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Objective: Tetrabenazine, a monoamine depleter and dopamine receptor blocker, is used to treat several hyperkinetic movement disorders. The authors studied the use of tetrabenazine for tardive dyskinesia. **Method:** Twenty patients with tardive dyskinesia (mean duration=43.7 months) were videotaped before and after tetrabenazine treatment. Randomized videotapes were scored with the motor subset of the modified Abnormal Involuntary Movement Scale (AIMS) by raters blind to pre- or posttreatment status. **Results:** One patient did not tolerate tetrabenazine owing to sedation. The remaining 19 were rated after a mean of 20.3 weeks at a mean tetrabenazine dose of 57.9 mg/day. There were significant improvements in mean scores on both the patient AIMS self-rating and the AIMS motor subset evaluated by the blind videotape raters. All 19 patients continued to take tetrabenazine after the study. **Conclusions:** Tetrabenazine was well tolerated and resulted in significant improvements in AIMS scores for patients with refractory tardive dyskinesia.

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Treatment of tardive dyskinesia is often unsatisfactory, especially in severe cases. A large number of treatments—including atypical neuroleptics, tocopherol, benzodiazepines, baclofen, calcium channel blockers, valproate, propranolol, opiates, cyproheptadine, tryptophan, lithium, manganese, niacin, and botulinum toxin—have been reported to improve tardive dyskinesia, usually in open-label trials (1, 2). None of these treatments, however, has consistently shown benefit in controlled trials.

Tetrabenazine inhibits presynaptic dopamine release and blocks postsynaptic dopamine receptors. It has been used for decades to treat a variety of hyperkinetic movement disorders, including tardive dyskinesia (3–9). Despite consistently impressive results, few data on efficacy have been published in the past 10 years. Furthermore, as a result of marketing and financial factors, the drug remains largely unavailable in the United States. We used randomized videotapes, scored by raters blind to pre- or posttreatment status, to test the efficacy of tetrabenazine for the treatment of tardive dyskinesia.

METHOD

Patients diagnosed with tardive dyskinesia who were referred to the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic were eligible. Most patients had tardive dyskinesia that was refractory to other medical treatments, but this was not a specific inclusion criteria. The diagnosis of tardive dyskinesia was based on 1) typical clinical appearance that was temporally related to the use of dopamine-receptor-blocking drugs and 2) the absence of other potentially culpable etiologies. Written informed consent was obtained from all patients after the medication was thoroughly discussed. The use of tetrabenazine was approved by the Baylor College of Medicine and Affiliates Institutional Review Board (IND number 16161).

The patients stopped taking the offending medications and any other treatments for tardive dyskinesia at least 30 days before they entered the study. Each patient then underwent a neurologic history and examination and was evaluated with the modified Abnormal Involuntary Movement Scale (AIMS) (10) by a single investigator (W.G.O.). Videotaping showed the patient while sitting (whole body and facial close-up), while talking, with arms stretched out forward, and while walking. Tetrabenazine was then started at a dose of 12.5 mg twice a day (25 mg) and then titrated to a maximum of 50 mg three times a day (150 mg) in weekly increments. The patient was instructed to stop increasing the dose if satisfactory benefit was experienced at the current dose or if adverse events became troublesome. The patients were not allowed to take any other treatments for tardive dyskinesia during the study period. The patients were instructed to return in approximately 3 months, but this interval varied owing to geographic constraints. During the reevaluation, each patient underwent global assessments, assessments of adverse events, neurologic examination with repeat AIMS evaluation, and identical videotaping.

Upon completion of enrollment, all videotapes (pretreatment and posttreatment) were randomized and coded. A separate investigator (P.A.H.), who was not involved with patient management and who was blind to treatment assignment (pretreatment versus posttreatment), rated these videotapes by using the motor section of the AIMS (questions 1–7). Audio was not allowed, since this could have jeopardized the blinding in several cases.

The primary data points were the score on the motor section of the AIMS (questions 1–7) derived from the blindly rated randomized

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videotapes, the subjective score on the AIMS (items 8–10), global impressions, and adverse events. Nonparametric data necessitated use of the Wilcoxon signed rank test to compare pretreatment and posttreatment scores.

RESULTS

Twenty patients were recruited; 15 were women, and the mean age was 65.2 years (SD=10.8, range=23–82). One 74-year-old woman with a 12-month history of haloperidol-induced tardive dyskinesia did not complete the follow-up evaluation because of sedation and stopped taking the medication after only 3 days. She was not included in the data analysis.

All but one patient had suffered from tardive dyskinesia for at least 6 months. The mean duration of tardive dyskinesia was 43.7 months (SD=47.1, range=2–420), and the mean exposure to the offending agent was 52.1 months (SD=46.1, range=1–240). The agents responsible for the tardive dyskinesia were metoclopramide (N=7), haloperidol (N=6), chlorpromazine (N=2), perphenazine (N=1), thiethylperazine (N=1), amoxapine (N=1), and fluphenazine (N=1). The underlying diagnoses resulting in the use of these medications were gastroenterologic disorders (N=7), unspecified psychosis (N=4), schizophrenia (N=3), agitation (N=3), organic brain disorder (N=2), and bipolar disorder (N=2). Two patients had two diagnoses each. Use of the offending medications was stopped in all cases. Eleven patients had noted no change after medication withdrawal, four noted worsening of their tardive dyskinesia, two had withdrawal-onset tardive dyskinesia, and for two patients the effects of medication withdrawal were unknown. In addition to their tardive dyskinesia, nine patients showed mild evidence of parkinsonism and five reported akathisia. The phenomenologic classifications of tardive dyskinesia were pure stereotypy (N=12), pure dystonia (N=1), and mixed stereotypy and dystonia (N=6). Fifteen of the patients had previously tried a total of 28 medications for tardive dyskinesia.

The patients underwent their second (posttreatment) evaluations at a mean of 20.3 weeks (SD=10.4) after starting tetrabenazine treatment. The mean tetrabenazine dose was 57.9 mg/day (SD=22.8). The mean score on the AIMS motor subset, determined by the blind raters from the videotapes, improved 54.2%, from 17.9 (SD=4.4) to 8.2 (SD=5.3) (two-tailed Wilcoxon signed rank, $p<0.001$). The subjective scores improved 60.4%, from a mean of 9.1 (SD=1.5) to 3.6 (SD=1.5) (two-tailed Wilcoxon signed rank, $p<0.001$). Eleven patients rated themselves as markedly improved, six as moderately improved, and two as mildly improved. No patient who completed the evaluation felt that the condition was unchanged or had worsened.

Aside from the one patient who withdrew, adverse events were never rated as more than mild by any patient. Sedation (five patients) was the only subjective complaint. Evidence of mild parkinsonism was found on neurologic examination in five patients.

DISCUSSION

In our single-blind randomized videotape assessment of tetrabenazine for the treatment of tardive dyskinesia, tetrabenazine was effective and generally well tolerated. The only patient for whom the blind videotape examination did not show improvement actually had a complete cessation of her oral-lingual stereotypy, but she developed a resting tremor that was rated as more severe on the blindly rated AIMS motor section.

Our results concur with those of open-label trials (11) and other smaller and older controlled studies (12–15). Furthermore, long-term data (16–18) suggest that the tetrabenazine benefit persists for the duration of use, without the development of tolerance. The adverse events were also similar to those previously documented (16). Sedation, parkinsonism, and depression are typically the most common limiting factors. These adverse events are, however, dose dependent and improve with dose reduction. Neuroleptic malignant syndrome and acute dystonic reactions have also been rarely noted (19, 20). An important feature of tetrabenazine is that, to our knowledge, tardive dyskinesia has never been reported as a complication of its use. In this way, tetrabenazine differs from other dopamine-receptor-blocking drugs, including atypical agents, which have been noted to occasionally cause tardive dyskinesia (21–23).

Tetrabenazine, a benzoquinolizine derivative, depletes presynaptic dopamine and serotonin storage and antagonizes postsynaptic dopamine receptors. Oral absorption is relatively poor and erratic (24). The serum half-life after oral ingestion is approximately 6 hours, but this is also highly variable (24). The drug subsequently undergoes first-pass metabolism to dihydrotetrabenazine, which appears to have similar pharmacological activity. Serum levels of this compound are much higher than levels of the parent compound, it is less protein bound, and the half-life is consistently around 10 hours. Therefore, it is possible that the majority of the clinical effect results from dihydrotetrabenazine. Individual response may also depend on specific monoamine transporter types (25).

Potential shortcomings of our clinical design include limitations of the video rating. This method tends to blunt subtle differences in movement, especially lingual movements, which are often only palpable. Therefore, it could tend to lessen differences in motor examinations and possibly weaken our results. Our patients were mostly referred from either psychiatrists or neurologists after not responding to conventional anti-tardive-dyskinesia treatment. Therefore, our study group may be biased toward more severe cases. The subjective results are also subject to the usual limitations of any open-label trial.

Given the fairly dramatic benefit shown in this and several older studies, and the relatively poor efficacy of traditional treatments for tardive dyskinesia, we feel that tetrabenazine should be considered in the treatment of severe and refractory cases of all types of tardive dyskinesia.

REFERENCES

1. Jankovic J: Tardive syndromes and other drug-induced movement disorders. Clin Neuropharmacol 1995; 18:197–214
2. Goetz CG: Tardive dyskinesia, in Movement Disorders. Edited by Watts R, Koller W. New York, McGraw-Hill, 1997, pp 519–526
3. Kang UJ, Burke RE, Fahn S: Natural history and treatment of tardive dystonia. Mov Disord 1986; 1:193–208
4. Jankovic J, Caskey TC, Stout JT, Butler IJ: Lesch-Nyhan syndrome: a study of motor behavior and cerebrospinal fluid neurotransmitters. Ann Neurol 1988; 23:466–469
5. Toglia JU, McGlamery M, Sambandham RR: Tetrabenazine in the treatment of Huntington's chorea and other hyperkinetic movement disorders. J Clin Psychiatry 1978; 39:81–87
6. Marti-Masso JF, Obeso JA: Coprolalia associated with hemiballismus: response to tetrabenazine. Clin Neuropharmacol 1985; 8:189–190
7. Jankovic J, Glaze DG, Frost JD: Effect of tetrabenazine on tics and sleep of Gilles de la Tourette's syndrome. Neurology 1984; 34:688–692
8. Jankovic J, Orman J: Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. Neurology 1988; 38:391–394
9. Swash M, Roberts AH, Zakko H, Heathfield KW: Treatment of involuntary movement disorders with tetrabenazine. J Neurol Neurosurg Psychiatry 1974; 35:186–191
10. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 534–537
11. Watson MW, Skelton D, Jamali F: Treatment of tardive dyskinesia: preliminary report on use of tetrabenazine. Can J Psychiatry 1988; 33:11–13
12. Asher SW, Aminoff MJ: Tetrabenazine and movement disorders. Neurology 1981; 31:1051–1054
13. Jankovic J: Treatment of hyperkinetic movement disorders with tetrabenazine: a double-blind crossover study. Ann Neurol 1982; 11:41–47
14. Kazamatsuri H, Chien C, Cole JO: Treatment of tardive dyskinesia: clinical efficacy of a dopamine-depleting agent, tetrabenazine. Arch Gen Psychiatry 1972; 27:95–99
15. Bartels M, Zeller E: Tetrabenazine (Nitoman) therapy of chronic spontaneous oral dyskinesia: a video- and EMG-controlled study. Eur Arch Psychiatry Neurol Sci 1984; 234:172–174
16. Jankovic J, Beach J: Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997; 48:358–362
17. Kazamatsuri H, Chien C-P, Cole JO: Long-term treatment of tardive dyskinesia with haloperidol and tetrabenazine. Am J Psychiatry 1973; 130:479–483
18. Mikkelsen BO: Tolerance of tetrabenazine during long-term treatment. Acta Neurol Scand 1983; 68:57–60
19. Petzinger GM, Bressman SB: A case of tetrabenazine-induced neuroleptic malignant syndrome after prolonged treatment. Mov Disord 1997; 12:246–248
20. Burke RE, Reches A, Traub MM, Ilson J, Swash M, Fahn S: Tetrabenazine induces acute dystonic reactions. Ann Neurol 1985; 17:200–202
21. Dave N: Clozapine-related tardive dyskinesia. Biol Psychiatry 1994; 35:886–887
22. Owens DG: Extrapyramidal side effects and tolerability of risperidone: a review. J Clin Psychiatry 1994; 55(May suppl):29–35
23. Walinder J, Holm AC: Experiences of long term treatment with remoxipride: efficacy and tolerability. Acta Psychiatr Scand Suppl 1990; 358:158–163
24. Roberts MS, McLean S, Millingen KS, Galloway HM: The pharmacokinetics of tetrabenazine and its hydroxy metabolite in patients treated for involuntary movement disorders. Eur J Clin Pharmacol 1986; 29:703–708
25. Peter D, Vu T, Edwards RH: Chimeric vesicular monoamine transporters identify structural domains that influence substrate affinity and sensitivity to tetrabenazine. J Biol Chem 1996; 271:2979–2986