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The Long-term Effect of Tetrabenazine in the Management of Huntington Disease

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Abstract

Objectives:
To enhance the knowledge on the long-term efficacy and safety of tetrabenazine (TBZ) in managing chorea.

Methods:
We analyzed 68 Huntington disease patients (mean disease duration, 55.8 ± 34.7 months) who had been treated with TBZ for a mean period of 34.4 ± 25.2 months (median, 34 months; mode, 48 months; range, 3–104 months). We measured the variation from pretreatment of the motor score of Unified Huntington's Disease Rating Scale at the first follow-up visit and at the latest.

Results:
Mean Unified Huntington's Disease Rating Scale–chorea underscore at the time of the pretreatment visit was 10.4 ± 4.1 (range, 0–28). At the first follow-up, 9.7 ± 7.8 months after the prescription of TBZ (mean dose, 35.3 ± 14.7 mg), mean score of chorea was 8.2 ± 4.1 (−21% compared with baseline), whereas at the latest follow-up visit (mean dose, 57.5 ± 14.7 mg), it was 9.5 ± 5.0 (9%). During the follow-up, the clinical benefit persisted, but the magnitude was reduced despite a progressive increase of the doses (up to 60%). Motor improvement was not influenced by sex, or doses or duration of therapy; age at onset was the only predictor of a good outcome. Five patients (7%) did not gain any improvement, and TBZ was discontinued. There were 2 withdrawals because of side effects; 34 patients reported at least 1 side effect.

Conclusions:
Tetrabenazine was well tolerated and produced long-term improvement of motor symptoms in Huntington disease patients, although a slight reduction of benefit occurred during the course of treatment.

Abbreviations: HD, Huntington disease, TBZ, tetrabenazine

Key Words: Huntington disease, tetrabenazine, therapy, chorea

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To date, the only treatment proven to be effective in the management of Huntington disease (HD) is symptomatic. Postsynaptic D2 receptor blockers (such as haloperidol, pimozide, tiapride, risperidone, olanzapine) are largely used for treating chorea and psychosis in HD patients.[1–3] Neuroleptics reduce chorea but may induce side effects on motor performance (inducing or worsening parkinsonism and akathisia), tardive dyskinesias, occasionally acute dystonia, and infrequently may also cause neuroleptic malignant syndrome. The sphere of affectivity might be worsened as well, with blunting of affect and apathy. Huntington disease patients seem to be more vulnerable than other patients to parkinsonism because hyperkinetic and hypokinetic movement disorders coexist as a consequence of the involvement of direct and indirect pathways in the basal ganglia-thalamus-cortical motor circuit.[4]

Tetrabenazine (TBZ) depletes presynaptic dopamine in the central nervous system, and to a lesser extent depletes norepinephrine and serotonin storage. Although in vitro studies have shown that TBZ blocks dopamine D2 receptors,[5] it only weakly inhibits the pharmacological action of the dopamine agonist apomorphine.[6] Therefore, it is unlikely that the weak D2 receptor antagonism might be responsible for TBZ clinical effects and, on the other hand, probably it gives reason for the absence of TBZ-induced tardive dyskinesias.[7] Tetrabenazine binds selectively and with high affinity to the central nervous system

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vesicular monoamine transporter (VMAT2), effectively depleting monoamines and serotonin from nerve terminals, by inhibiting their transport into presynaptic vesicles. Dopamine is preferentially depleted over norepinephrine or serotonin.[8] The highest binding density for TBZ is in the caudate nucleus, putamen, and nucleus accumbens—areas known to bear the brunt of pathology in HD. The VMAT binding (and monoamine depletion) by TBZ is reversible, lasts for hours, and is not modified by chronic treatment.[9]

After the early use of TBZ as an antipsychotic in the 60s,[10] it has been used in the treatment of different dyskinesias.[11] To date, several reports have suggested that TBZ ameliorates hyperkinetic movement disorders, in particular, HD-associated chorea.[12–25] However, literature data are scanty, and the number of controlled studies is limited possibly because the drug is not registered in most countries.[26–30]

The purpose of this study was to retrospectively evaluate an unselected population of HD patients treated for a long period with TBZ to have data on efficacy and safety. The source of data was a retrospective review of clinical charts. To our knowledge, this series represents the largest number of HD patients followed up for a long-term period.

METHODS

This is a retrospective analysis of patients with HD followed up at the Movement Disorder Clinic of the Gemelli Hospital in Rome. The diagnosis of HD was confirmed by expanded CAG repeat testing in *IT-15* gene or, when the genetic test was unavailable, was considered definite when the following 3 criteria were satisfied: (1) typical clinical presentation, (2) the family tree indicating autosomal dominant inheritance, and (3) mutation of *IT-15* gene at least in 1 family member. We selected for further analysis all patients treated with TBZ. In our center, HD patients are examined routinely twice a year; each evaluation includes neurological history and examination, a motor assessment performed by means of the motor section of the Unified Huntington's Disease Rating Scale (UHDRS).[31]

In all of the patients with phenotypes dominated by choreic dyskinesias, TBZ was introduced at very tiny doses: 6.25 mg BID or TID (12.50–18.75 mg/d) and slowly titrated up to a maximum of 50 mg TID (150 mg/d), on the basis of weekly increments. For the analysis, the following data have been considered: age, sex, age at onset of HD, therapy duration, maximum benefit achieved, maximal dose received, side effects, concomitant treatments, and change in chorea score after the first TBZ dose prescribed and at last evaluation.

Continuous data were expressed as mean (±SD), compared by one-way analysis of variance and Student *t* test, and correlated by means of Pearson correlation coefficient. Correlations between ranked data were assessed with Spearman rank order correlation and multivariate regression analysis.

RESULTS

Seventy-four patients with HD were, or had been, under treatment with TBZ; 6 of them were lost at follow-up, so we considered for further analysis 68 patients (35 women and 33 men) with at least 1 follow-up visit after the prescription of TBZ. Their mean age at onset was 43.3 ± 11.8 years; mean disease duration was 55.8 ± 34.7 months (range, 12–168 months). The HD diagnosis was confirmed by means of genetic analysis of *IT-15* gene in 30 patients (mean number of CAG repeats on the expanded allele, 46.15 ± 5.1; range, 41–64). Mean UHDRS motor score at the time of the first visit was 39.4/120 ± 14.5 (range, 14–68). Mean score of the dystonia section was 3.5/20 ± 2.9 (range, 0–10); mean score of the chorea section was 10.4/28 ± 4.1 (range, 3–18). They were treated with TBZ for an average of 34.4 ± 25.2 months (median, 34 months; mode, 48 months; range, 3–104 months); at the moment of data collection,

TABLE 1. Mean UHDRS Motor Score, Mean Chorea Subscore, and Mean Dystonia Subscore at Baseline, at the First Follow-up Visit, and at the Latest Visit of TBZ Ongoing Treatment

	Baseline	First Visit (variation compared with baseline)	*P*	Latest Visit (variation compared with baseline)	*P*
Mean UHDRS motor score, range	39.4 ± 14.5, 14–68	39.8 ± 14.7, 12–78 (+1%)	NS	52.3 ± 18.0, 13–85 (+32%)	0.005
Mean chorea subscore, range	10.4 ± 4.1, 3–18	8.2 ± 4.1, 0–20 (–21%)	0.00005	9.5 ± 5.0, 1–22 (−9%)	NS
Mean dystonia subscore, range	3.5 ± 2.9, 0–10	2.6 ± 2.1, 0–8 (−25%)	NS	4.8 ± 3.4, 0–13 (+37%)	NS

Mean UHDRS motor score (range, 0–120), mean chorea subscore (range, 0–28), and mean dystonia subscore (range, 0–20) at baseline, at the first follow-up visit (9.7 ± 7.8 months after TBZ was prescribed; mean dose, 35.3 ± 14.7 mg), and at the latest visit (after 34.4 ± 25.2 months) of TBZ ongoing treatment (mean dose, 57.5 ± 14.7 mg).
NS indicates not significant.

46 patients (68%) were still under treatment. Mean dose at first follow-up, after 9.7 ± 7.8 months, was 35.3 ± 14.7 mg (mode and median of 37.5 mg; range, 6.25–75 mg). Mean dose at the latest follow-up was 57.5 ± 14.7 mg (mode of 75 mg and median of 50; range, 6.25–150 mg). The mean maximal dose reached was 64.3 ± 35.0 mg (median of 62.5 mg; range, 6.25–150 mg).

Effect on Motor Symptoms

When compared with the baseline visit, at the first follow-up (9.7 ± 7.8 months later), chorea was significantly improved (mean chorea subscore was reduced by 21%; $P = 0.00005$); mean UHDRS motor score was unchanged, and mean dystonia subscore was reduced by 25%, but the difference with the baseline scores failed to reach statistical significance (see Table 1 and Figure 1).

When compared with the baseline evaluation, at the latest follow-up visit performed after 34.4 ± 25.2 months, HD was progressed, as revealed by a significant increase of the mean UHDRS motor score (+32%; $P = 0.005$); the mean score of

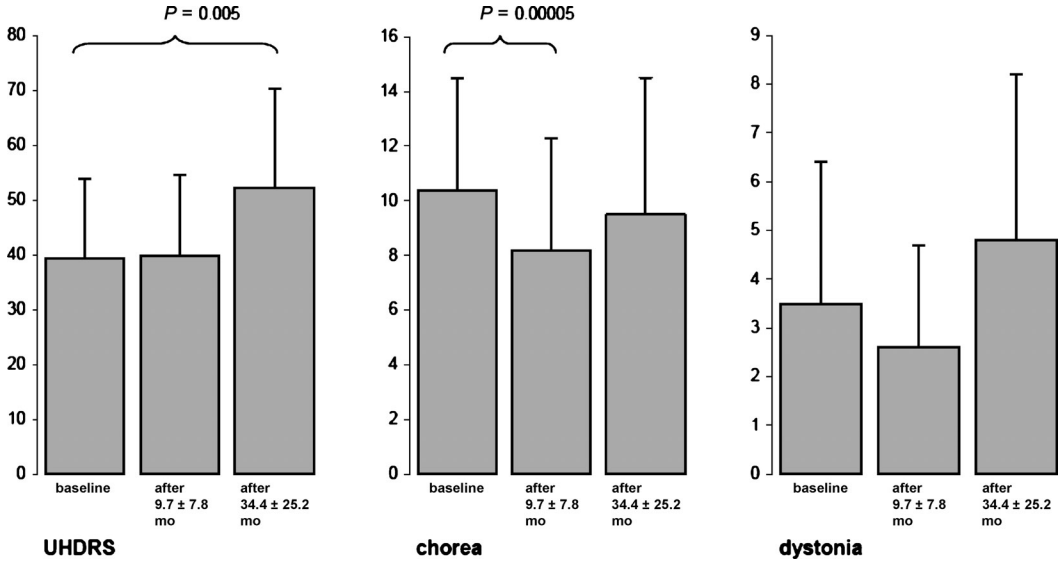

FIGURE 1. Mean UHDRS motor score, score of the chorea section, and score of the dystonia section at the time of the first visit, at the first follow-up visit (9.7 ± 7.8 months later; mean dose, 35.3 ± 14.7 mg), and at the latest follow-up visit (34.4 ± 25.2 months later; mean dose, 57.5 ± 14.7 mg).

dystonia section was increased by 37%, and the mean score of the chorea section was reduced by 9% (see Table 1 and Figure 1). The improvement was reduced by 13% when compared with the first follow-up ($P < 0.01$), notwithstanding mean dose increase of 63% ($P < 0.01$).

Of 68 patients treated with TBZ, 5 (7%) did not gain any improvement of chorea and withdrew TBZ.

We analyzed the predictors of TBZ-induced improvement of chorea: TBZ dose, sex, age at the moment of treatment, and therapy duration were not related to a good outcome, whereas an older age at onset predicted a better outcome ($\beta = 0.33$, 0.33, and 0.38 for the first and last evaluations, and at the maximum effect achieved, respectively; $P < 0.01$).

Side Effects

During the overall duration of treatment, 34 patients (50%) reported at least 1 side effect: drowsiness (n = 17), depression (n = 11), disturbances of gut function (diarrhea, constipation, nausea, vomiting or abdominal pain) (n = 8), worsening of parkinsonism (n = 4), xerostomia (n = 2), and hypotension (n = 1). Tetrabenazine was generally well tolerated because only 2 subjects withdrew TBZ due to side effects: rapid worsening of psychiatric disturbance and disabling asthenia. The incidence of side effects was not dose related. During the course of the disease, while the drug was still ongoing, concomitant treatments were required for several patients: in 57 patients, an antiparkinsonian drug (mostly amantadine added to TBZ with the aim of preventing TBZ-induced parkinsonism), 47 benzodiazepines, 34 typical neuroleptics, 13 quetiapine or clozapine, and 35 antidepressants.

DISCUSSION

Previous studies on small series documented the efficacy of TBZ: in 10 patients with HD followed up for about 18 months, the average improvement of chorea was 2.6 (on a scale of 0–5: 1, marked improvement; 4, no response; 5, worsening).[22] In another long-term series, the global response rating of 1 (marked improvement) was recorded in 82.8% of 29 patients with HD (average duration of TBZ treatment, 28.9 months).[23] In a single-blind trial of TBZ in 18 patients with HD, 14 patients subjectively rated themselves as markedly (n = 7) or moderately improved (n = 7).[24] In the first and unique multicentric, prospective, double-blind, placebo-controlled, dose-finding, 12-week study of TBZ for the treatment of chorea in HD, the drug adjusted up to 100 mg/d significantly reduced chorea burden of 23.5% compared with placebo, improved global outcome, and was generally safe and well tolerated.[30] A post hoc analysis of chorea response by dosage in this study indicates that subjects whose TBZ dosage was 50 mg/d or less had a greater improvement in chorea at week 12 than did those receiving more than 50 mg/d. Differences in susceptibility to TBZ caused by hepatic processing, avidity of VMAT-2, or other unknown factors may account for this finding. As stated by the authors themselves, because the study was only 12 weeks long, they cannot draw inferences about TBZ-related adverse effects that may occur after more prolonged exposure.[30]

This study has several limitations, the main is the open-label fashion and the concomitant use of other medications possibly interfering with the motor features of the patients. Even if we recognize the limits of a study based on the review of clinical charts, without any prospective design, we thought it may be worthy to share our experience on a relatively large HD population treated with TBZ. Our data confirm the efficacy of TBZ in reducing chorea in HD patients, albeit we did not find that dosages greater than 50 mg/d were less effective than lower doses as previously reported.[30] Motor improvement was not influenced by doses, duration of therapy, or sex; age at onset was the only predictor of a good outcome:

patients with later onset have a better outcome. This observation is of interest. Because a previous study failed to observe a relation between outcome and CAG repeats,[30] we hypothesize that a different phenotype (chorea was more pronounced than dystonia in late-onset HD[32]) or the products of still unidentified regulatory genes (which might also influence age at onset[33]) may influence the response to antidyskinetic drugs in HD patients. Besides this, our long-term observation reveals that along time, the dosages were progressively increased, but higher doses were not sufficient to maintain the benefit achieved initially: at the latest available visit, there was a moderate reduction of clinical benefit. This observation might be explained by the progressively increasing severity of motor and nonmotor symptoms caused by disease progression. In favor of this hypothesis, it has to be outlined that UHDRS global motor score and dystonia score were rated as more severe at the latest follow-up, whereas chorea was unchanged compared with baseline. As HD is a neurodegenerative disease, it is difficult to say that the extent of this loss of benefit on chorea was caused by a decrease of TBZ efficacy or by disease progression.

The safety of long-term TBZ therapy in HD has been recently confirmed by Kenney and colleagues,[34] who performed a retrospective chart review on 448 patients (98 with chorea) treated with TBZ for a mean of 2.3 ± 3.4 years: common side effects included drowsiness (25.0%), parkinsonism (15.4%), depression (7.6%), and akathisia (7.6%); all were dose related and abated when dosage was reduced. In our series, no case of akathisia was recorded in contrast to previous observations; the drug was generally well tolerated, and side effects (drowsiness, worsening of parkinsonism, depression) were easily managed, reducing the dose or adding antidepressants or antiparkinsonian drugs. Only in 2 patients did side effects cause drug withdrawal.

Several questions remain open: (1) Is TBZ to be considered the first-line strategy in controlling chorea in HD? (2) Is it superior to typical/atypical neuroleptics? (3) Do concomitant treatments with antidepressant/antiglutamatergic drugs influence outcome or progression of motor symptoms? (4) Because the acute effect of TBZ on chorea in HD patients has been recently investigated (the maximum effects achieved was 163 ± 59 minutes after the administration of the drug),[35] is it possible to predict the chronic effect of the drug, settling a test challenge? These topics need to be addressed in well-designed long-term studies because the quality of life of HD patients might dramatically improve for several years, especially when chorea is the presenting symptom, and cognitive and psychiatric functions are spared.

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