Analysis of CYP2D6 Genotype and Response to Tetrabenazine

Mehanna R, Hunter C, Davidson A, Ondo W, Jimenez-Shahed J, Jankovic J

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

INTRODUCTION

- Tetrabenazine (TBZ) is approved by the US Food and Drug Administration (FDA) for the treatment of chorea associated with HD, but has also been found to be an effective treatment for other hyperkinetic movement disorders (1-3).
- Active metabolites of TBZ are metabolized via the cytochrome P450 enzyme system (CYP). The CYP2C9, CYP2C19 and CYP2D6 enzymes facilitate about 30% of P450-mediated drug metabolism (4).
- CYP2D6 genotyping is recommended for patients prescribed >50 mg/day of TBZ, but its clinical implications on the dosing of TBZ have not been well studied.
- We therefore examined the CYP2D6 phenotype of patients treated with TBZ and its impact on clinical response and care.

METHODS

- Phenotypes are defined as follows:
  - **Poor metabolizer (PM)**: lack the functional enzyme; more likely to develop side effects because of high plasma levels.
  - **Intermediate metabolizer (IM)**: heterozygous for one deficient allele or carry two alleles with reduced activity.
  - **Extensive metabolizer (EM)**: possess two normal alleles.
  - **Ultra-rapid metabolizer (UM)**: multiple gene copies; are likely to experience only short-term effects from the drug because of fast metabolism.
- CYP2D6 genotyping was performed on sequential subjects treated with TBZ
  - o Results were not known to the treating physician at the time of TBZ initiation or titration.
- CYP2D6 and CYP2C19 genotypes were determined using the FDA-approved AmpliChip CYP-450 test which predicts a phenotype as poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM) and ultra-rapid metabolizers (UM).
- A reviewer blinded to CYP2D6 phenotype retrospectively reviewed charts for the indication for TBZ, titration, total daily dose, response rating scores and frequency and severity of adverse events. Data was extracted to a database for analysis.
- **Statistical methods**
  - o Correlation coefficients were calculated within each group to search for any possible correlations between age, sex, total daily dose (mg), duration of titration to the optimal dose (weeks), adverse effects, metabolizer status and response to treatment using a previously described Global Response Scale (15)(score range from 1 to 5; 1 = marked improvement and 5 = marked worsening).
  - o Correlations between continuous variables were calculated with Pearson's correlation coefficient; for categorical data Spearman's rank correlation coefficients were used.
  - o One-way analysis of variance was performed using metabolizer status as the independent variable relative to each of duration of titration, total daily dose, and treatment response.
  - o Post-estimation regression with EM metabolizer status as the constant value was performed to determine relationships between type of metabolizer and each of response to treatment, weeks of titration and dose.

RESULTS

- 127 patients were tested with mean age 42.7 ± 23.4 years and 76(59.8%) males.
- UM patients required a *higher average daily dose* [137.5 vs. 62.9(EM), 66.1(IM) and 40.9 mg (PM) respectively; p = 0.004 UM vs EM,IM,PM] and *longer titration* (8 weeks vs. 3.3(EM), 4.4(IM) and 3.0(PM); p <0.01) to achieve *optimal benefit* (best possible efficacy with no or tolerable side effects).
- Treatment response was less in the IM group [2.2 vs. 1.2(PM), 1.3(EM) and 1.5(UM); only comparison to EM was significant (p=0.047)].
- The PM group had a higher rate of sedation [66% vs. 27.3(IM), 20(EM) and 50(UM)], akathisia [11% vs. 5(IM), 9(EM) and 0(UM)], insomnia [11% vs. 9(IM), 5(EM) and 0(UM)] and suicidality [11% vs. 9(IM), 2.5(EM) and 0(UM)], but none of these differences reached statistical significance.
- Parkinsonism, found in 9% of the IM group compared to 8.8% in the EM group and 0% in each of the UM and PM groups, did not significantly correlate with the genotype (Figure 2).

Table 1: Demographics, Dosing, and Response.

	UM	EM	IM	PM	Pvalue
Number of patients (%)	2 (1.6%)	100 (78.7%)	14 (11.0%)	11 (8.7%)	
Sex (M/F)	2/0	60/40	6/8	8/3	
Age (Years) ±SD	35.6 ±26.0	41.0 ± 23.6	50.5 ± 22.8	48.9 ± 21.6	NS
Total Daily Dose ±SD	137.5 ±88.4	62.9 ±35.5	66.1 ± 23.7	40.9 ± 19.4	P<0.01 (ANOVA-UM vs. EM,IM,PM)
Titration (Weeks) ±SD	8.0 ±0.0	3.3 ±1.2	4.4 ± 2.3	3.0 ±0.8	P<0.01 (ANOVA-UM vs. EM,IM,PM)
Treatment Response	1.5 ±0.7	1.5 ±0.7	2.1 ±1.4	1.4 ±0.5	0.047 (ANOVA-IM vs. EM,PM,UM)
Adverse Events (%)	1 (50%)	45 (56%)	12 (110%)	12 (133%)	NS

Fig 1: Diagnostic categories:

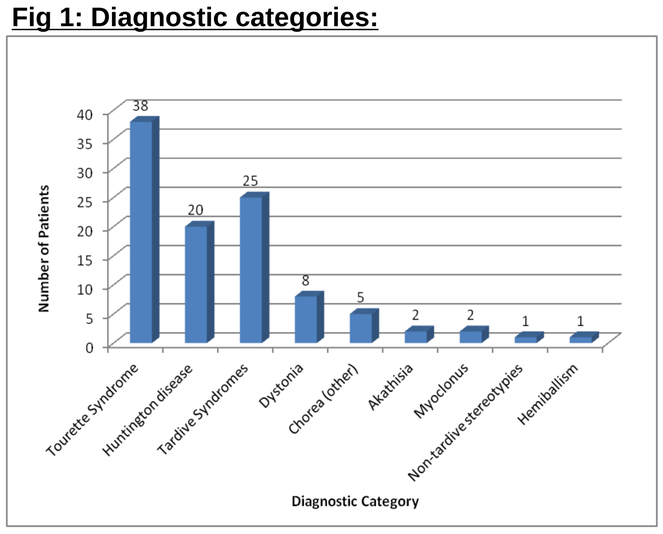
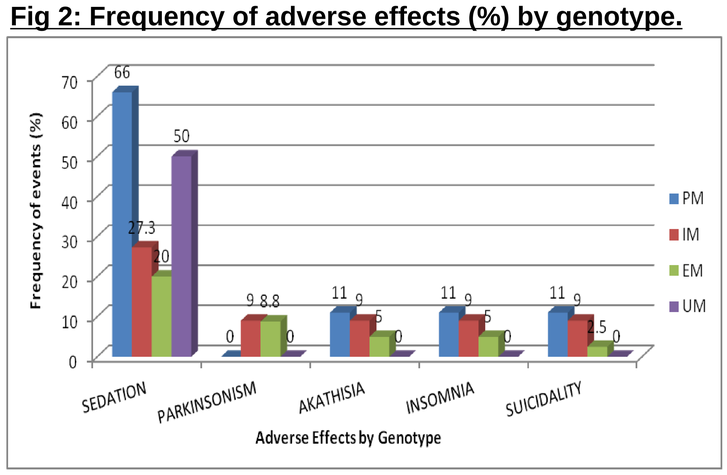


Fig 2: Frequency of adverse effects (%) by genotype.



DISCUSSION

As expected, the majority of our patients were categorized as EM (78.7%, Table 1).

- *Daily dose:* The UM group required a higher average daily dose than the other 3 groups, but contained only 2 subjects so it was not statistically significant. As might be expected, the duration of titration to the optimal dose was significantly longer in the UM group compared to each of the other groups.
- *Clinical response:* The response was best in the PM group and significantly worse in the IM group when compared to the EM group. The difference in treatment response is difficult to interpret because patients were titrated to their optimal dose [best possible efficacy with no or tolerable adverse effects (4)], rather than to a fixed dose. Interestingly, the PM patients had the best response despite having the smallest mean daily dose, possibly reflecting slower TBZ metabolism.
- *Adverse effects:*
- The EM group had the highest absolute number of adverse effects; the PM and IM groups experienced the same number of adverse effects; the UM group experienced only one adverse effect. The highest rate was in the PM group (133%) despite having the smallest daily dose, possibly because of a slower metabolism and higher serum concentration of TBZ metabolites. The lowest rate was in the UM group(50%), presumably because of their fast metabolism and lower concentrations of TBZ metabolites.
- Side effects/patient were more frequent in the PM group, followed by the IM>EM >UM group. While these results are consistent with our expectations, they were non-significant.
- Correctly predicting the individual response, dose or adverse effects related to a drug based on the CYP2D6 genotype may be quite difficult. Some have suggested that poor or rapid metabolizers may not derive optimal benefit from drugs if metabolism via CYP2D6 or other cytochrome P-450 enzymes occurs (5-8) while others have found little or no evidence for recommending genotyping for patients taking such drugs or even to avoid enzyme inhibitors (9-12).

CONCLUSION

In our cohort, clinical benefit remained high (1.4-2.1) on our 5-point response rating scale and side effects were in keeping with the known potential side effects of TBZ. More importantly, these side effects were readily clinically apparent. In no circumstance was knowledge of CYP2D6 genotype or phenotype required to manage a patient's condition.

In light of these results, and while acknowledging that larger, prospective studies will provide a more definitive assessment of the relationship between CYP2D6 genotypes and clinical response, we suggest that the recommendation to genotype all patients prescribed more than 50mg/day of TBZ should be reconsidered.

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