Evaluation of the Potential for Concomitant Medications to Affect Valbenazine Pharmacokinetics

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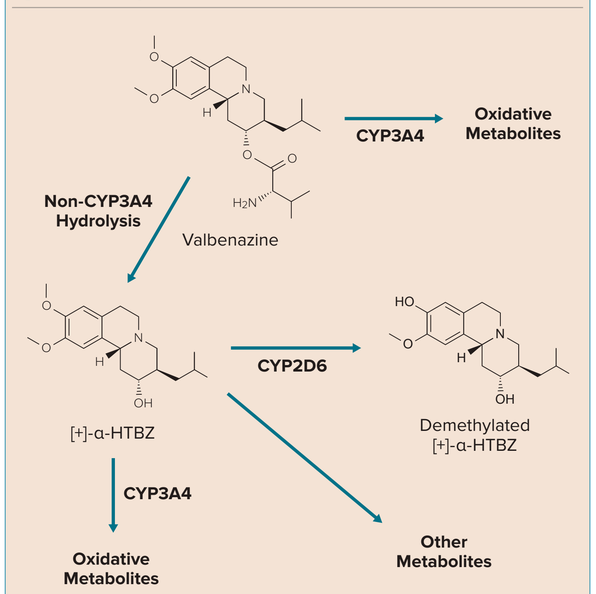
BACKGROUND

- Valbenazine (INGREZZA) is a novel vesicular monoamine transporter 2 (VMAT2) inhibitor that is approved in the US for the treatment of tardive dyskinesia (40 or 80 mg, once-daily) and is in development for the treatment of Tourette syndrome[1]
- Valbenazine is converted to an active metabolite, [+]-α-dihydrotetrabenazine ([+]-α-HTBZ; also referred to as (2R,3R,11bR)-dihydrotetrabenazine or O-desvalylvalbenazine), through the loss of L-valine by hydrolysis (**Figure 1**)[2]
- The potential for concomitant medications to affect valbenazine and [+]-α-HTBZ pharmacokinetics (PK) was assessed through *in vitro* and clinical studies

Figure 1. Summary of Valbenazine Metabolism



METHODS

IN VITRO STUDIES

- Valbenazine and [+]-α-HTBZ were incubated with cDNA-expressed cytochrome P450 (CYP) enzymes. The rate of clearance of valbenazine and [+]-α-HTBZ and formation of metabolites was monitored using HPLC-MS/MS
- The effects of CYP-selective antibodies, and the selective CYP3A4/5 and CYP2D6 inhibitors, azumulin and quinidine, respectively, on valbenazine and/or [+]-α-HTBZ clearance and metabolite formation were determined using pooled human liver microsomes and/or cryopreserved human hepatocytes
- Valbenazine and [+]-α-HTBZ permeability and potential to be P-gp substrates were determined in Caco-2 and/or MDCK-MDR1 cell monolayers

CLINICAL STUDIES

- Ketoconazole (strong CYP3A4 inhibitor) single-center, open-label study
  - The potential for concomitant ketoconazole to affect valbenazine and [+]-α-HTBZ PK was evaluated in 24 healthy subjects
  - Subjects received a single dose of valbenazine 50 mg on Day 1 (Reference) and Day 6 (Test)
  - On Days 5 to 9, a twice-daily regimen of ketoconazole 200 mg was administered
  - Blood samples for determining plasma valbenazine and [+]-α-HTBZ concentrations were obtained prior to and out to 96 hours following each valbenazine dose
- Rifampin (strong CYP3A4 inducer) single-center, open-label study
  - The potential for concomitant rifampin to affect valbenazine and [+]-α-HTBZ PK was evaluated in 12 healthy subjects
  - Subjects received a single dose of valbenazine 80 mg Day 1 (Reference) and Day 11 (Test)
  - On Days 5 to 14, a once-daily regimen of rifampin 600 mg was administered
  - Blood samples for determining plasma valbenazine and [+]-α-HTBZ concentrations were obtained prior to and out to 96 hours following each valbenazine dose
- Effect of potent CYP2D6 inhibitors: data from a Phase 3 clinical trial[1]
  - Plasma samples for determination of plasma valbenazine and [+]-α-HTBZ concentrations were obtained at Weeks 2, 4, and 6 from patients with tardive dyskinesia (TD) and a psychiatric diagnosis (i.e., schizophrenia/schizoaffective disorder, mood disorder) who received once-daily valbenazine 40 or 80 mg for 6 weeks
- Bioanalytical and statistical methods (all 3 clinical studies)
  - Plasma valbenazine and [+]-α-HTBZ concentrations were determined using validated HPLC-MS/MS methods
  - PK parameters were determined using standard non-compartmental methods
  - For the ketoconazole and rifampin studies, statistical analyses were conducted by determining the point estimate and two-sided 90% confidence interval (CI) for Test to Reference (T/R) differences of log-normalized PK parameters
  - In the Phase 3 study, dose-normalized plasma concentrations of valbenazine and [+]-α-HTBZ at Weeks 2, 4, and 6 in the subgroup of patients prescribed concomitant potent CYP2D6 inhibitors (paroxetine, fluoxetine, duloxetine, sertraline, or bupropion) were compared by t-test to respective concentrations in patients not receiving a CYP2D6 inhibitor

RESULTS

IN VITRO STUDIES

- Valbenazine was primarily metabolized to [+]-α-HTBZ by non-CYP-mediated hydrolysis and to oxidative metabolites by CYP3A4
- [+]-α-HTBZ was primarily metabolized by CYP2D6 and CYP3A4
- Valbenazine and [+]-α-HTBZ were highly membrane permeable
- Valbenazine and [+]-α-HTBZ were not P-gp substrates

CLINICAL STUDIES

- Coadministration of valbenazine with ketoconazole, a strong CYP3A4 inhibitor, resulted in increased peak (C_{max}) and overall (AUC) exposure to valbenazine and [+]-α-HTBZ (**Figure 2, Figure 4**)
- Coadministration of valbenazine with rifampin, a potent CYP3A4 inducer, resulted in decreased peak and overall exposure to valbenazine and [+]-α-HTBZ (**Figure 3**, **Figure 4**)
- Mean (±SD) dose-normalized valbenazine concentrations were similar (*P*=0.249) with (3.375±2.037 ng/mL/mg) or without (3.683±2.360 ng/mL/mg) concomitant CYP2D6 inhibitors (**Figure 5A**)
- Mean dose-normalized [+]-α-HTBZ concentrations were also similar (*P*=0.571) with (0.534±0.321 ng/mL/mg) or without (0.513±0.326 ng/mL/mg) concomitant CYP2D6 inhibitors (**Figure 5B**)

Figure 2. Valbenazine and [+]-α-HTBZ Plasma Concentrations With and Without Concomitant Ketoconazole

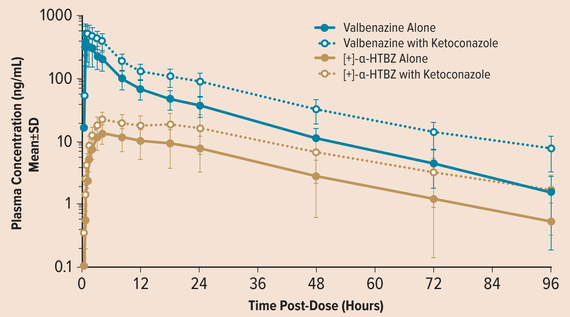


Figure 3. Valbenazine and [+]-α-HTBZ Plasma Concentrations With and Without Concomitant Rifampin

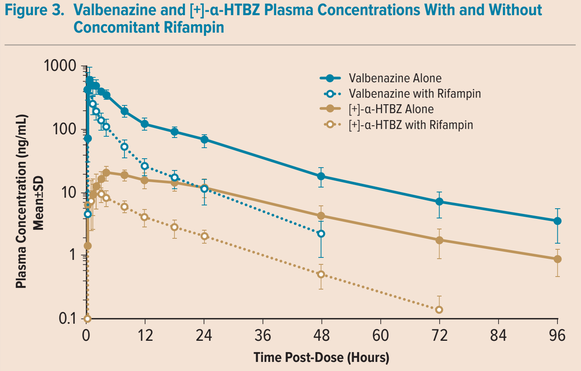


Figure 4. Summary of the Effect of Ketoconazole and Rifampin on Valbenazine and [+]-α-HTBZ PK Parameters

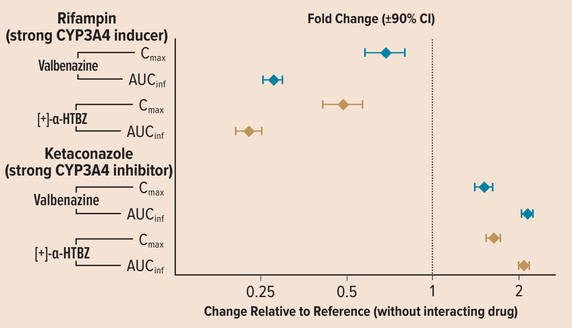
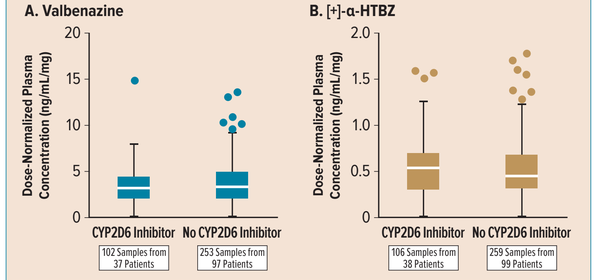


Figure 5. Mean Dose-Normalized Valbenazine and [+]-α-HTBZ Concentrations During a Phase 3 Study in Subjects with Tardive Dyskinesia



Boxes represent the interquartile range (IQR): lower edge (25th percentile), upper edge (75th percentile), horizontal bar (median). Whiskers extend beyond the box to ≤1.5 x IQR. Values outside the whiskers are plotted as individual data points.

DISCUSSION

- Coadministration of valbenazine with P-gp inhibitors is not anticipated to affect valbenazine or [+]-α-HTBZ PK
- *In vitro* and *in vivo* data consistently demonstrate CYP3A4 is involved in the metabolism of valbenazine and [+]-α-HTBZ
  - Due to the potential for increased exposure, a valbenazine dose reduction should be considered in patients coadministered valbenazine with a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin)
  - Due to the potential for reduced concentrations, coadministration of potent CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) with valbenazine is not recommended
- Although [+]-α-HTBZ was metabolized by CYP2D6 *in vitro*, plasma [+]-α-HTBZ concentrations in patients prescribed concomitant potent CYP2D6 inhibitors were similar to concentrations in patients not receiving a potent CYP2D6 inhibitor
  - Nonetheless, a valbenazine dose reduction may be considered based on tolerability when coadministering valbenazine with a potent CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, quinidine)

CONCLUSIONS

- Clear dosing recommendations to avoid concomitant use with potent CYP3A4 inducers and to reduce valbenazine dose with CYP3A4 inhibitors allow for ease of management with valbenazine treatment in clinical practice have been developed[3]
- While CYP2D6 metabolism contributes to elimination of [+]-α-HTBZ, a clinically-relevant effect of potent CYP2D6 inhibitors on [+]-α-HTBZ PK was not apparent in a Phase 3 trial; nonetheless, patient tolerability should be monitored when potent CYP2D6 inhibitors are coadministered with valbenazine

REFERENCES

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2. Grigoriadis DE, Smith E, Hoare SR, et al. *J Pharmacol Exp Ther*. 2017;361:454-61.
3. INGREZZA [prescribing information]. San Diego, CA: Neurocrine Biosciences, Inc., 2017.

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