Evaluation of Potential Drug Interactions With Valbenazine

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BACKGROUND

- Valbenazine (INGREZZA™), a highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor, is approved in the US for the treatment of tardive dyskinesia (40 or 80 mg, once-daily)[1]
- Valbenazine is converted to an active metabolite, [+]-α-dihydrotetrabenazine ([+]-α-HTBZ) through the loss of L-valine by hydrolysis[2]
- The potential for valbenazine to affect the pharmacokinetics (PK) of concomitant medications and for concomitant medications to affect valbenazine and [+]-α-HTBZ PK was assessed through *in vitro* and clinical studies

IN VITRO STUDIES

METHODS AND RESULTS: BACKGROUND STUDIES FOR VALBENAZINE

Methods	Results
Valbenazine as Perpetrator	
Potential inhibition of common cytochrome P450 (CYP) drug metabolizing enzymes was assessed by incubating valbenazine and [+]-α-HTBZ with human liver microsomes and determining IC_{50} values for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 metabolism of CYP-selective probe substrates	Valbenazine and [+]-α-HTBZ were weak direct inhibitors of CYP2D6, but IC_{50} values greatly exceed typical therapeutic exposures; all other CYP IC_{50} values were greater than 9600 ng/mL; no time-dependent inhibition of CYP enzymes by valbenazine and [+]-α-HTBZ was observed
CYP induction was evaluated in fresh primary-cultured hepatocytes from 3 donors by measuring CYP1A2, CYP2B6 and CYP3A4/5 metabolism of probe substrates following incubation with valbenazine and [+]-α-HTBZ for 3 days	Neither valbenazine nor [+]-α-HTBZ induced CYP enzyme activity
Drug transporter inhibition was assessed by incubating valbenazine and [+]-α-HTBZ in cell-based test systems expressing OAT1, OAT3, OCT2, OATP1B1, OATP1B3 transporters and determining IC_{50} values for transport of probe substrates; P-gp and BCRP inhibition was assessed by determining IC_{50} for flux of probe substrates across MDCK-MDR1 and Caco-2 cell monolayers, respectively	Valbenazine was a weak inhibitor of P-gp transport (IC_{50}: 9950 ng/mL), but no other clinically-relevant effects of valbenazine or [+]-α-HTBZ on drug transporter activity were observed
Valbenazine as Victim	
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	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
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	Valbenazine and [+]-α-HTBZ were highly membrane permeable Valbenazine and [+]-α-HTBZ were not P-gp substrates

CLINICAL STUDIES

METHODS

- Single-center, open-label studies were conducted to evaluate potential drug-drug interactions with valbenazine (**Table 1**)
- Bioanalytical and statistical methods
  - Plasma drug concentrations were determined using validated HPLC-MS/MS methods
  - PK parameters were determined using standard non-compartmental methods
  - Statistical analyses were conducted by determining the point estimate and two-sided 90% confidence intervals (CI) for Test to Reference (T/R) differences of log-normalized PK parameters

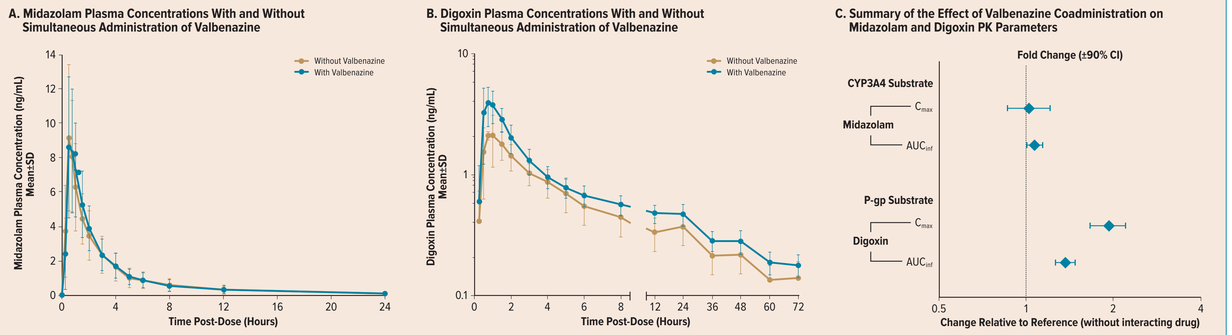
Table 1. Summary of Clinical Studies

	Study 1 (N=12)	Study 2 (N=24)	Study 3 (N=24)	Study 4 (N=12)
Perpetrator	Valbenazine	Valbenazine	Ketoconazole (strong CYP3A4 inhibitor)	Rifampin (strong CYP3A4 inducer)
Victim	Midazolam (sensitive CYP3A4 substrate)	Digoxin (sensitive P-gp substrate)	Valbenazine [+]-α-HTBZ	Valbenazine [+]-α-HTBZ
Reference day/test day Victim dose	Day 1 / Day 4 Midazolam 2 mg	Day 1 / Day 16 Digoxin 0.5 mg	Day 1 / Day 6 Valbenazine 50 mg	Day 1 / Day 11 Valbenazine 80 mg
Perpetrator regimen	Day 4 Valbenazine 80 mg	Days 10-16 Valbenazine 80 mg	Days 5-9 Ketoconazole 200 mg	Days 5-14 Rifampin 600 mg
Blood sample collection	Prior to and out to 48h following each midazolam dose	Prior to and out to 72h following each digoxin dose	Prior to and out to 96h following each valbenazine dose	Prior to and out to 96h following each valbenazine dose

RESULTS

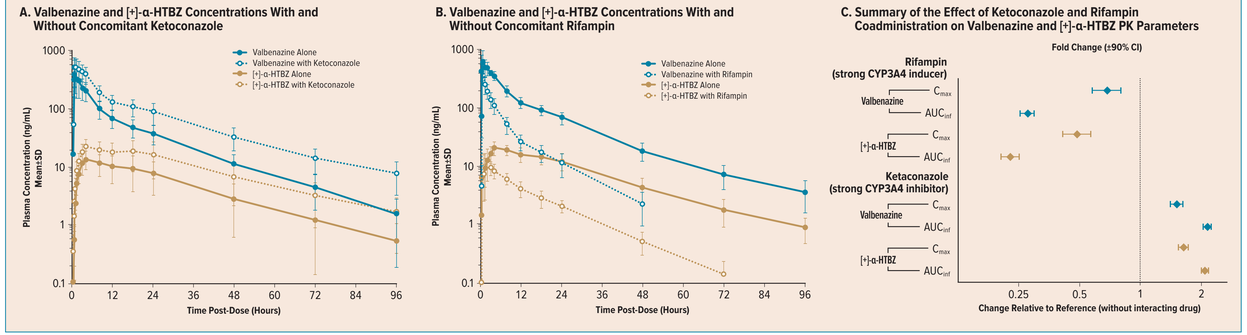
- Valbenazine as perpetrator **(Figure 1)**
  - Study 1: Coadministration of valbenazine with midazolam did not affect midazolam PK
  - Study 2: Coadministration of valbenazine with digoxin resulted in increased digoxin C_{max} and AUC, without impacting digoxin $t_{1/2}$

Figure 1. Effects of Valbenazine on Digoxin and Midazolam Pharmacokinetics



- Valbenazine as victim **(Figure 2)**
  - Study 3: Coadministration of valbenazine with ketoconazole resulted in increased peak (C_{max}) and overall (AUC) exposure to valbenazine and [+]-α-HTBZ
  - Study 4: Coadministration of valbenazine with rifampin resulted in decreased peak and overall exposure to valbenazine and [+]-α-HTBZ

Figure 2. Effects of Ketoconazole and Rifampin on Valbenazine Pharmacokinetics



DISCUSSION

VALBENAZINE AS PERPETRATOR

- Valbenazine and [+]-α-HTBZ have a low potential to affect CYP-mediated metabolism of concomitant medications
- With the exception of increased absorption of sensitive P-gp substrates, valbenazine and [+]-α-HTBZ have a low potential to affect the transport of concomitant medications that are substrates for common drug transporters
- Simultaneous administration of valbenazine and digoxin resulted in an increased rate (C_{max}) and extent (AUC) of digoxin absorption, without impacting digoxin elimination ($t_{1/2}$)
  - The effect on digoxin absorption is believed to result from the high GIT valbenazine concentrations immediately following oral ingestion that inhibit P-gp in the GIT
  - Plasma valbenazine concentrations are much lower than the P-gp IC_{50}; therefore, consistent with the lack of effect on digoxin $t_{1/2}$, systemic inhibition of P-gp is not anticipated
  - Simultaneous oral administration of valbenazine and sensitive P-gp substrates that are not typically completely absorbed may result in increased absorption of the P-gp substrate

VALBENAZINE AS VICTIM

- Coadministration of valbenazine with P-gp inhibitors is not anticipated to affect valbenazine or [+]-α-HTBZ PK
- 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
- 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[3]; nonetheless, patient tolerability should be monitored when coadministered with potent CYP2D6 inhibitors

CONCLUSIONS

- Dose adjustments to valbenazine should be based primarily on clinical efficacy and tolerability assessment
- Co-administration with potent CYP3A4 inhibitors may require adjusting valbenazine dose in clinical practice (80 mg to 40 mg), and CYP3A4 inducers may lower valbenazine exposure and effect
- Apart from potential increased absorption of P-glycoprotein substrates, valbenazine showed minimal potential to affect CYP-mediated metabolism of co-medications and low potential to affect pharmacokinetics of drug transporter substrates

REFERENCES

1. Ingrezza [prescribing information]. San Diego, CA: Neurocrine Biosciences, Inc., 2017.
2. Grigoriadis DE, Smith E, Hoare SR, et al. *J Pharmacol Exp Ther.* 2017;361:454-61.
3. Loewen G, Luo R, Smith EB, Liang GS, Bozigian H, O'Brien CF. Poster presented at the American Society of Clinical Psychopharmacology; May 29-June 2, 2017; Miami, FL. Abstract W61.

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