Evaluation of the Potential for Valbenazine to Elicit Drug Interactions

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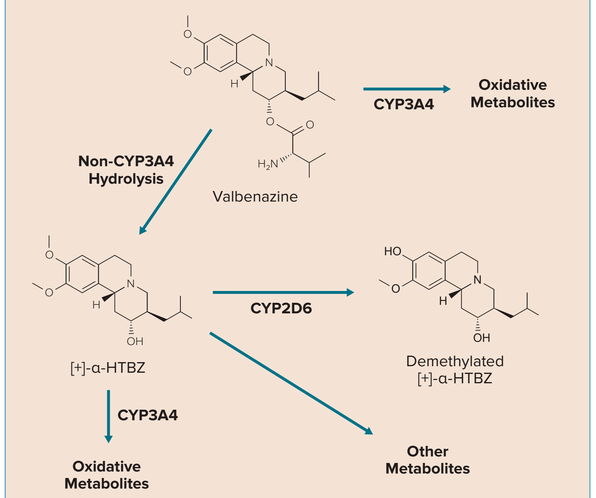
BACKGROUND

- Valbenazine (INGREZZA) is a vesicular monoamine transporter 2 (VMAT2) inhibitor recently 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 valbenazine to affect the pharmacokinetics (PK) of concomitant medications was assessed through *in vitro* and clinical studies

Figure 1. Summary of Valbenazine Metabolism



METHODS

IN VITRO STUDIES

- 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. A 30-minute preincubation was used to assess time-dependent inhibition
- 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
- 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

CLINICAL STUDIES

- Midazolam (sensitive CYP3A4 substrate): single-center, open-label study
  - The potential for valbenazine to affect midazolam PK was evaluated in 12 healthy subjects
  - Subjects received a single dose of midazolam 2 mg on Day 1 (Reference) and Day 4 (Test)
  - On Day 4, subjects also received a single dose of valbenazine 80 mg concurrent with the midazolam dose
  - Blood samples for determining plasma midazolam concentrations were obtained prior to and out to 48 hours following each midazolam dose
- Digoxin (sensitive P-gp substrate): single-center, open-label study
  - The potential for valbenazine to affect digoxin PK was evaluated in 24 healthy volunteers
  - Subjects received a single dose of digoxin 0.5 mg on Day 1 (Reference) and Day 14 (Test)
  - On Days 10-16, subjects also received a single dose of valbenazine 80 mg
  - Blood samples for determining plasma digoxin concentrations were obtained prior to and out to 72 hours following each digoxin dose
- Bioanalytical and statistical methods (both clinical studies)
  - Plasma midazolam and digoxin 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

RESULTS

IN VITRO STUDIES

- Valbenazine and [+]-α-HTBZ were weak direct inhibitors of CYP2D6, but IC_{50} values greatly exceeded typical therapeutic exposures (**Table 1**); 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
- Neither valbenazine nor [+]-α-HTBZ induced CYP enzyme activity
- Valbenazine was a weak inhibitor of P-gp transport (IC_{50}: 9950 ng/mL; **Table 1**), but no other clinically-relevant effects of valbenazine or [+]-α-HTBZ on drug transporter activity were observed

Table 1. Summary of Valbenazine and [+]-α-HTBZ Inhibition of CYP Enzymes and Drug Transporters and Associated Clinical Safety Margins

CYP Enzyme/ Transporter	Valbenazine		[+]-α-HTBZ	
	IC_{50} (μM)	Clinical Margin[a]	IC_{50} (μM)	Clinical Margin[a]
CYP1A2	>50	>37	>50	>417
CYP2C9	>50	>37	>50	>417
CYP2C19	>50	>37	>50	>417
CYP2D6	9.0	6.7	14.2	118
CYP3A4/5	31.1	23.2 0.04[b]	>50	>417
CYP2B6	>30	>37	>30	>250
CYP2C8	>30	>37	>30	>250
CYP2E1	>30	>37	>30	>250
OAT1	>25	>18	>5	>41.7
OAT3	>25	>18	>5	>41.7
OCT2	>25	>18	>5	>41.7
OATP1B1	>25	>18	>5	>41.7
OATP1B3	>25	>18	>5	>41.7
BCRP	>100	>74	>5	>41.7
P-gp	23.8	17.8 0.03[b]	>5	>41.7

[a]Clinical safety margin determined using projected mean steady-state total plasma C_{max} values of 556 ng/mL (1.34 μM) and 39.0 ng/mL (0.12 μM) for valbenazine and [+]-α-HTBZ, respectively, based on population PK model. Margins based on free drug concentrations would be greater based on 1% and 39% plasma free fractions, respectively.
[b]Clinical safety margin for inhibition of gastrointestinal wall CYP3A4/5 and P-gp, based on 320,000 ng/mL (770 μM) representing complete dissolution of an 80 mg dose in 250 mL of gastrointestinal fluid.

CLINICAL STUDIES

- Coadministration of valbenazine with midazolam did not affect midazolam PK (**Table 2**, **Figure 2**, **Figure 4**)
- Coadministration of valbenazine with digoxin resulted in increased digoxin C_{max} and AUC, without impacting digoxin $t_{1/2}$ (**Table 2**, **Figure 3**, **Figure 4**)

Table 2. Summary of the Effect of Valbenazine Coadministration on Select Midazolam and Digoxin PK Parameters

Concomitant Medication	Parameter	With Valbenazine Mean (SD)	Without Valbenazine Mean (SD)	Ratio (90% CI)[a]
Midazolam	C_{max} (ng/mL)	9.61 (3.83)	9.59 (4.10)	1.02 (0.86, 1.21)
	AUC_{inf} (ng*h/mL)	24.9 (11.5)	23.7 (12.3)	1.07 (1.00, 1.14)
	$t_{1/2}$ (h)	4.7 (2.3)	4.5 (2.1)	ND
Digoxin	C_{max} (ng/mL)	4.61 (1.47)	2.47 (0.989)	1.92 (1.66, 2.21)
	AUC_{inf} (ng*h/mL)	41.0 (7.38)	30.9 (9.25)	1.36 (1.26, 1.48)
	$t_{1/2}$ (h)	35 (7.2)	36 (7.4)	ND

[a]Ratio and 90% confidence interval (CI) of geometric least-squares means based on a mixed model using log-transformed data.
ND: not determined.

Figure 2. Midazolam Plasma Concentrations With and Without Simultaneous Administration of Valbenazine

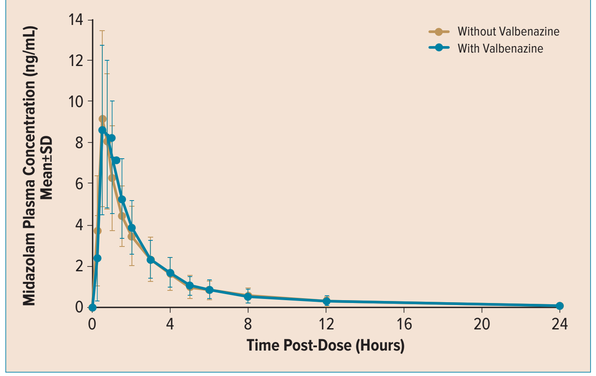


Figure 3. Digoxin Plasma Concentrations With and Without Simultaneous Administration of Valbenazine

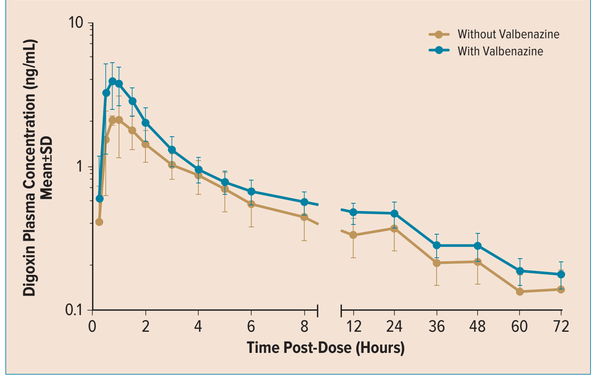
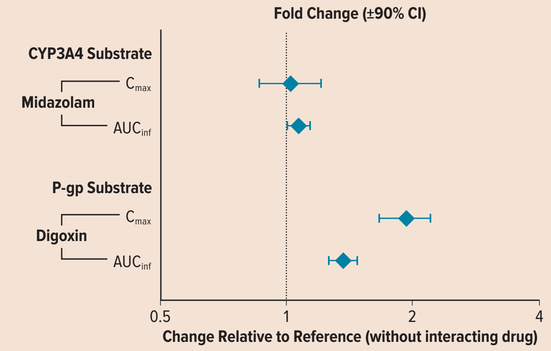


Figure 4. Summary of the Effect of Valbenazine Coadministration on Midazolam and Digoxin PK Parameters



DISCUSSION

- Valbenazine and [+]-α-HTBZ have a low potential to affect CYP-mediated metabolism of concomitant medications
- Despite high gastrointestinal tract (GIT) concentrations, no evidence for GIT wall inhibition of CYP3A4/5 metabolism of midazolam was observed
- With exception of P-gp transport, 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 of 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

CONCLUSIONS

- Valbenazine has minimal potential to affect CYP-mediated metabolism of concomitant medications
- Apart from potential increased gastrointestinal absorption of sensitive P-gp substrates, valbenazine has a low potential to affect the PK of concomitant medications that are drug transporter substrates

REFERENCES

1. Hauser RA, Factor SA, Marder SR, et al. *Am J Psychiatry.* 2017;174:476-84.
2. Grigoriadis DE, Smith E, Hoare SR, et al. *J Pharmacol Exp Ther.* 2017;361:454-61.

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