## PI-103

HALOPERIDOL METABOLITES INHIBIT CYP2D6 CATALYZED DEXTROMETHORPHAN O-DEMETHYLATION IN VITRO. J.G. Shin, MD, PhD, K. Kane, D.A. Flockhart, MD, PhD, Division of Clinical Pharmacology, Georgetown University Medical Center, Washington, DC 20007.

Haloperidol is known for its clinically significant interaction with drugs that are metabolized by CYP2D6, but the clinical effect was not sufficiently explained by the in vitro CYP2D6 inhibitory potency of haloperidol itself due to its low therapeutic concentration. To evaluate the involvement of haloperidol metabolites in drug interactions with CYP2D6 substrates, several haloperidol metabolites were assessed for their inhibitory effect on CYP2D6 catalyzed dextromethorphan O-demethylation using human liver microsomes and human cDNA-expressed CYP2D6 in vitro. Reduced haloperidol, N-dealkylated metabolites CPHP and FBPA competitively inhibited the CYP2D6 catalyzed reaction, while the inhibition by pyridinium metabolite HPP was best explained by noncompetitive inhibition model with nonlinear regression analysis. Estimated mean $K_i$ values of these metabolites were comparable with that of haloperidol (Table).

| Haloperidol Metabolites | Type of Inhibition | $K_i$ |
|---|---|---|
| Haloperidol | Partial Competitive | 7.2 |
| Reduced Haloperidol | Partial Competitive | 0.5 |
| CPHP | Competitive | 22.9 |
| FBPA | Competitive | 338.3 |
| HPP+ | Noncompetitive | 1.5 |

These data suggest that most haloperidol metabolites have strong inhibitory effect of CYP2D6 catalyzed reaction like haloperidol and these metabolites may play an important role in the haloperidol drug interaction with CYP2D6 substrates. These data also increase our understanding of haloperidol structure–CYP2D6 inhibition relationship.

## PI-104

REPEATED ADMINISTRATIONS OF AMISULPRIDE (A) DO NOT MODIFY LITHIUM CARBONATE (L) PHARMACOKINETICS IN HEALTHY VOLUNTEERS. S. Chaufour,* MD, N.G. Borgstein,* MD, W. Van den Eynde,* MD, F. Bernard,* PhD, M. Canal,* PharmD, I. Zieleniuk,* MD, J.L. Pinquier,* MD, Synthélabo, France and Belgium, Pharma Bio Research, Zuidlaren, The Netherlands.

A is a substituted benzamide neuroleptic, which blocks selectively dopamine D2 and D3 receptors. As its main route of elimination is renal, the pharmacokinetics of co-administered lithium was tested. A double blind, randomized, placebo (P) controlled study including 2 parallel groups of 12 healthy male volunteers was conducted to assess the potential interaction of A on the safety and pharmacokinetics of L. Each volunteer received L 500 mg bid for 14 days and either A 100 mg bid or P from day 8. Sequential plasma and urinary samples were taken for L and A determination. Split-plot analysis and ANOVA were respectively performed for L and A. Both treatments were well tolerated. No statistically significant variation of plasma levels and renal clearance of L were observed:

| day 14 | Cmax (mmol/L) | AUC(0-12) (mmol h/L) | $CL_R$ (L/h) |
|---|---|---|---|
| L | 0.929 ±0.033 | 7.42 ±0.28 | 1.69 ±0.09 |
| L+A | 0.835 ±0.029 | 7.02 ±0.35 | 1.93 ±0.13 |

The co-administration of A 100 mg bid during 7 days with L 500 mg bid does not modify the safety and pharmacokinetics of L in healthy volunteers.

## PI-105

IN VIVO INHIBITION OF MIDAZOLAM DISPOSITION BY KETOCONAZOLE AND FLUOXETINE, AND COMPARISON TO IN VITRO PREDICTION. Y.W.F. Lam, PharmD, L. Ereshefsky, PharmD, C. Alfaro, PharmD, Michael Miller, MD, Dept of Pharmacology and Psychiatry, Univ TX Hlth Sci Ctr at San Antonio.

The effect of ketoconazole (K) and fluoxetine (F) on oral midazolam (M) disposition was evaluated in 24 healthy subjects in a parallel study design. M clearance was decreased by 770 ±620% after K (200 mg/d × 11 days), in contrast to a negligible increase (17.6 ±15.9%) after F (60 mg × 5d, then 20 mg/d). The corresponding changes in Cmax of M were 280.9 ±231.4% increase with K, and 23.2 ±51.6% increase with F.

To evaluate how these *in vivo* results related to *in vitro* inhibition findings, the M AUC ratio (AUC in the presence of K or F/AUC in their absence) in the subjects were compared to the predicted decrement in M clearance calculated using literature values of *Ki* and *Km*, the Cmax of M, and the achievable in vivo plasma concentrations of K, F, and norfluoxetine (NF).

The AUC ratio in the presence of K was 8.7 ±6.2; and 0.82 ±0.16 in the presence of F. Using achievable Cmax of M (9× difference) and inhibitor concentrations (40-fold range for K, 4-fold range for F and NF), and literature values of *Km* and *Ki*, the predicted % inhibition of M clearance was 57.7 ±23.5% for K, 0.4 ±0.1% for F, and 1.8 ±0.5% for NF.

## PI-106

MULTIPLE SITE INTERACTION OF TRIAZOLAM AND KETOCONAZOLE IN MICE: ROLE OF P-GLYCOPROTEIN. L.L. von Moltke,* B.W. Granda,* J.M. Grassi,* and D.J. Greenblatt, Tufts University, Boston, MA.

Systemic kinetics, brain uptake, and behavioral effects of triazolam (TRZ) and ketoconazole (KET), given alone and in combination, were studied in: mice (X) deficient in expression of the multidrug transporter protein, P-glycoprotein (P-gp), corresponding to the *mdr1a* gene [*mdr1a (-/-)* or *mdr1ab (-/-)*]; and in matched control mice (C) with normal P-gp expression [*mdr1a/b (+/+)*]. After 0.175 mg/kg TRZ I.P., C and X mice did not differ in mean serum TRZ (12.7 and 8.7 ng/ml) or in whole brain TRZ (33.1 and 34.0 ng/gm). After 50 mg/kg KET I.P., serum KET did not differ between C and X mice (56 vs 48 μg/ml), but whole brain KET was greatly increased in X mice (24 vs 52 μg/gm), explained by deficient outward transport of KET due to lack of blood-brain barrier P-gp. Cotreatment with TRZ and KET caused a large increase in serum TRZ (10.7 vs 94 ng/ml) and in whole-brain TRZ (34 vs 203 ng/gm) compared to TRZ alone; this interaction was identical in C and X groups. Compared to vehicle control, TRZ alone depressed computer-determined stereotypic behavior to a nearly identical extent (41 units down to 26 units) in both C and X mice. KET alone had a smaller and nonsignificant depressant effect (33 units). In C mice, the TRZ + KET combination greatly augmented the depressant effect of TRZ (down to 13 units), whereas in X mice, TRZ effects were actually blunted (30 units) by addition of KET despite elevated plasma and brain TRZ levels. Thus the kinetics, brain uptake and depressant effects of TRZ are not altered in X mice, nor is the kinetic interaction with KET. However brain uptake of KET is significantly increased in X mice, blunting the behavioral effects of the interaction with TRZ, probably because of benzodiazepine receptor occupancy by KET.