PII-17

ELEVATED ORAL CLEARANCE OF VERAPAMIL IN CYP3A5 EXPRESSERS. Y. Jin, MD, Y. Wang, PhD, M. A. Hamman, MS, R. Marunde, BS, Z. Hu, MD, PhD, J. Hilligoss, S. D. Hall, PhD, Indiana University, Indianapolis, IN.

BACKGROUND/AIMS: Verapamil, a CYP3A4 substrate and inhibitor *in vivo*, is a more potent mechanistic inhibitor of CYP3A4 than CYP3A5 *in vitro*. We hypothesized that the clearance of verapamil would be different in subjects genetically capable of expressing CYP3A5 compared to non-expressers.

METHODS: Twenty healthy subjects with predetermined CYP3A5 genotype were recruited. CYP3A5 *3, *6 and *7 genotypes were determined with real-time PCR. After an outpatient course of verapamil 240 mg per day for 7 days, verapamil pharmacokinetics were determined on days 8 and 9. Serum concentrations of R- and S-verapamil and R- and S-norverapamil were determined with by chiral LC/MS. Verapamil pharmacokinetics parameters were derived from non-compartmental analysis (WinNonlin). Differences in the pharmacokinetic parameters among subjects with different CYP3A5 genotypes were tested with Student's *t* tests (SPSS v12).

RESULTS: CYP3A5 expressers (subjects with at least one *1 allele) had a statistically higher orally clearance for R and S verapamil (table 1). There is a trend towards lower R- and S- verapamil Cmax in subjects who were CYP3A5 expressers. CYP3A5 genotype did not influence the R to S verapamil AUC ratio.

CONCLUSIONS: CYP3A5 expressers may experience diminished pharmacological effect of verapamil due to a greater steady-state oral clearance in this group.

Table 1. Effect of CYP3A5 Expression on Verapamil Pharmacokinetics

	Expressers (N = 10)	Non-expressors (N=10)	P Value
R-verapamil			
Cmax (ng/ml)	155.3 ± 28.7	282.5 ± 54.3	0.053
Cl/F (L/hour)	172.1 ± 27.8	94.3 ± 12.4	0.02
S-verapamil			
Cmax (ng/ml)	32.2 ± 6.9	67.2 ± 16.1	0.061
Cl/F (L/hour)	925.1 ± 162.7	473.7 ± 81.5	0.02
AUC ratio			
R/S Verapamil	5.3 ± 0.3	4.7 ± 0.3	0.21

PII-18

ESTROGEN RECEPTOR GENOTYPES ARE ASSOCIATED WITH RESPONSE OF SERUM CHOLESTEROL TO TAMOXIFEN TREATMENT. N. I. Ntukidem, MD, L. Li, PhD, M. I. Rehman, MD, T. C. Skaar, PhD, Y. Jin, MD, Z. Desta, PhD, A. M. Storniolo, MD, V. Stearns, MD, D. F. Hayes, MD, D. A. Flockhart, MD, PhD, Indiana University, University of Michigan, Indianapolis, IN.

BACKGROUND: Breast cancer and non-tumoral responses during tamoxifen treatment are variable; and this variability may be genetic.

METHODS: We prospectively followed 185 breast cancer patients on tamoxifen therapy. Serum lipid analyses were performed in Clinical Laboratories at baseline and after 4 months of treatment. Genetic variants in the estrogen receptors α [rs#2234693, (PvuII) and rs#9340799 (XbaI)] and β [rs#1256049 (ESR2-01) and rs#4986938(ESR-02)] were analyzed.

RESULTS: Tamoxifen significantly lowered cholesterol (−24.2 mg/dl) and LDL (−26.9mg/dl) compared to baseline. Women with the ER PvuII CC allele had a 2-fold greater decrease in total cholesterol when compared to women with CT/TT alleles (P=0.01). The premenopausal women with the AA/AG alleles of ERα XbaI had a lower baseline total (204 vs. 244 mg/dl; P=0.012,) and LDL cholesterol (116 vs.150mg/d; p=0.0l) compared to women with the GG alleles. There was no association between baseline cholesterol and the XbaI polymorphism in postmenopausal women. In a multivariate analysis, grouping the subjects according to their combined ERα and ERβ genotypes, the subgroup with ER α PvuII CC and any ESR2-02 allele combination had the greatest reduction in total cholesterol concentration in response to tamoxifen when compared to women with ER α CT/TT and any ESR2-02 (P=0.0032).

CONCLUSIONS: Estrogen receptor genotypes are associated with baseline cholesterol and the response of serum cholesterol to tamoxifen treatment in breast cancer.