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INHIBITION OF SN-38 GLUCURONIDATION BY KETOCONAZOLE. W. Yong, MBChB, J. Ramirez, MS, F. Innocenti, MD, PhD, M. J. Ratain, MD, University of Chicago, Chicago, IL.

BACKGROUND/AIMS: Ketoconazole has been shown to inhibit the glucuronidation of the UGT2B7 substrates AZT and lorazepam. Its effect on UGT1A substrates is unknown. A recent study (Kehrer et al, J Clin Oncol, 2002) found that co-administration of irinotecan and ketoconazole led to a significant increase in the formation of SN-38. This study investigates whether ketoconazole contributes to the increase in SN-38 formation by inhibiting SN-38 glucuronidation.

METHODS: SN-38 glucuronidation activities were determined by measuring the rate of SN-38 glucuronide (SN-38G) formation using pooled human liver microsomes (HLM) and cDNA transfected UGT1A isoforms (1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9) in the presence of ketoconazole. Indinavir, a known UGT1A1 inhibitor, was used as a positive control. SN-38G formation was measured by HPLC.

RESULTS: A 20% reduction in SN-38G formation was observed after incubation of HLM with SN-38 and ketoconazole at 10 μM ($p=0.001$). Among the UGT1A isoforms screened, ketoconazole showed the highest inhibitory effect on UGT1A1 and UGT1A9, reducing SN-38 glucuronidation activities by 59% and 32% ($p<0.05$), respectively. The IC50 values (using UGT1A1 and UGT1A9) were 8.8 μM and 6.3 μM for ketoconazole, respectively.

CONCLUSION: These results suggest that ketoconazole is a potent UGT1A1 and UGT1A9 inhibitor. Further work is currently being undertaken to establish the possible mechanism of ketoconazole-mediated inhibition of SN-38 glucuronidation.

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CYP2J2 METABOLIZES DOMPERIDONE IN GUINEA PIG HEARTS. V. Michaud, MSc, R. Massé, PhD, J. Turgeon, PhD, Université de Montréal, MDS Pharma Services, Montréal, PQ, Canada.

BACKGROUND: We have shown previously that domperidone is metabolized mainly by the CYP3A4/5 isozymes. Recent studies have indicated that CYP2J2 is abundant in cardiovascular tissues. Preliminary data from our laboratory indicate that guinea pig heart microsomes have the capacity to metabolize domperidone.

PURPOSES: The objective of this study was to identify the cytochrome P450 isoforms involved in the metabolism of domperidone in guinea pig hearts.

METHODS: *In vitro* incubations were conducted with microsomes from baculovirus transfected cells expressing high levels of CYP2J2 (rCYP2J2) and microsomes from guinea pig hearts. Domperidone (1–500 μM) and testosterone (300 μM) were incubated for 45 and 30 minutes, respectively, with various microsomal preparations in the presence of NADPH regenerating system. Formation rate of domperidone major hydroxylated metabolite (M3) and 6βOH-testosterone were monitored by HPLC with fluorescence and UV detection, respectively.

RESULTS: Km and Vmax values for the formation of M3-domperidone were 5 μM and 1.44 nmol/nmolCYP450/min, when incubations were performed with rCYP2J2. Similarly, M3-domperidone was formed in incubations performed with guinea pig heart microsomes. But, in contrast, no 6βOH-testosterone was detected in experiments conducted with heart microsomes.

CONCLUSIONS: CYP2J2, in addition to CYP3A4/5 shows catalytic activity towards domperidone. These results suggest the involvement of CYP2J2 in the metabolism of domperidone in the heart.

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GRAPEFRUIT JUICE INHIBITS CYP2A6 AND NICOTINE METABOLISM. J. Hukkanen, MD, PhD, N. L. Benowitz, MD, University of California, San Francisco, San Francisco, CA.

BACKGROUND/AIMS: Grapefruit juice is a strong inhibitor of CYP3A4 leading to clinically important interactions. The aim was to study the effect of grapefruit juice on the metabolism of nicotine, primarily a CYP2A6 substrate.

METHODS: 10 volunteers were given 2 mg oral dose of deuterium-labeled nicotine on three occasions together with 1 L of water, grapefruit juice or half-strength grapefruit juice in randomized order. Nicotine and metabolites were analyzed in plasma and urine for 8 hours.

RESULTS: Grapefruit juice inhibited the formation of cotinine from nicotine ($AUC_{COT\ 0-8hr}$ 6807 vs. 7805 vs. 8007 min*ng/ml, grapefruit juice, diluted grapefruit juice, and water, respectively, $p < 0.05$). T_{max} of cotinine was delayed, and C_{max} lower with grapefruit juice than with water (T_{max} 216 vs. 159 vs. 147 min, $p < 0.05$, C_{max} 18 vs. 21 vs. 22 ng/ml, $p < 0.05$). Grapefruit juice increased renal clearance of nicotine compared to water (231 vs. 123 ml/min, $p < 0.05$). Other pharmacokinetic parameters of nicotine were not affected.

CONCLUSIONS: Grapefruit juice inhibits the metabolism of nicotine to cotinine, a pathway mediated by CYP2A6. The inhibition is modest, and the effect on total nicotine clearance was offset by the increase in the renal clearance of nicotine. However, the inhibition of CYP2A6 by grapefruit juice may be of clinical significance with other drugs metabolized by CYP2A6.

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ASSESSMENT OF PHARMACOKINETIC INTERACTIONS BETWEEN EZETIMIBE AND CYCLOSPORINE. A. Bergman, PhD, A. Johnson-Levonas, PhD, J. Burke, MS, P. Larson, MS, L. Zaru, PhD, L. Reyderman, PhD, P. Statkevich, PhD, T. Kosoglou, PharmD, G. Murphy, MD, K. Gottesdiener, MD, J. Paolini, MD, PhD, Merck & Co. Inc., Schering-Plough Research Institute, Blue Bell, PA.

AIMS: Dyslipidemia is often under-treated in patients on cyclosporine (CyA) due to potentially clinically significant statin drug interactions. Thus, the pharmacokinetic (PK) interactions between the intestinal cholesterol absorption inhibitor ezetimibe (EZE) and CyA were explored.

METHODS: Study 1: 1 period in 8 renal transplant (txp) patients with normal renal function to assess single-dose (SD) total EZE (EZE + EZE-glucuronide) $AUC_{0\text{-}last}$ (120h sampling) and C_{max} of EZE 10 mg during steady-state CyA (75–150 mg b.i.d.). Study 2: 2-period crossover in 12 healthy subjects to assess SD $AUC_{0\text{-}last}$ (48h sampling) and C_{max} of CyA alone (100 mg) and after multiple doses (MD) of EZE 20 mg/d x7d.

RESULTS: Study 1: Total EZE $AUC_{0\text{-}last}$ and C_{max} were 3.4- and 3.9-fold higher ($p \leqq 0.001$), respectively, in txp patients on CyA versus historical healthy controls ($N=17$) but did not exceed the highest AUC observed in patients given 50 mg/d in prior EZE MD PK studies. Study 2: MD EZE 20 mg increased CyA $AUC_{0\text{-}last}$ by 15%; 90% CI (7%, 25%) was within prespecified similarity bounds. No significant difference in CyA C_{max} was observed ($p>0.050$). EZE and CyA were well-tolerated in both studies.

CONCLUSIONS: The clinical significance of these findings is unknown. Although the mean EZE AUC with CyA is within bounds of exposures in prior MD PK studies, the long-term clinical safety implications have not been determined. EZE + CyA should be managed with appropriate caution and monitoring of CyA levels.