PI-56

INFLUENCE OF RITONAVIR BOOSTED LOPINAVIR ON CYTOCHROME P450 2D6 ACTIVITY IN HIV INFECTED AND HEALTHY INDIVIDUALS. A. Jetter, MD, C. Wyen, MD, D. Frank, MSc, R. Aarnoutse, PhD, T. Klaassen, MSc, F. Abdulrazik, BSc, D. Burger, PhD, G. Fätkenheuer, MD, U. Fuhr, MD, Department of Pharmacology, Clinical Pharmacology, University of Cologne, Department I of Internal Medicine, University of Cologne, Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Cologne, Germany.

BACKGROUND/AIMS: Ritonavir (RTV) is used as an inhibitor of CYP3A4 to increase the bioavailability of lopinavir (LPV). In addition, we examined the effect of RTV boosted LPV on CYP2D6 activity in 30 HIV infected patients and 12 healthy controls.

METHODS: Patients got 30 mg dextromethorphan (DEX) as part of a 3 drugs phenotyping cocktail before and 14 days after starting an antiretroviral therapy containing 400 mg LPV + 100 mg RTV bid. In a randomized manner, 12 healthy males got the same phenotyping cocktail with and without a single dose of 400 mg LPV + 100 mg RTV. In plasma collected up to 12 h after dosing, DEX and dextrorphan (DOR) were analyzed using LC-MS/MS (LOQ 0.10 ng/mL for both analytes). Changes in CYP2D6 activity were assessed using a bioequivalence approach.

RESULTS: In patients, the geometric mean DEX $AUC_{0\text{-}INF}$ increased from 25.6 ng/mL*h (geom. coefficient of variation [CV] 287%) to 33.6 ng/mL*h (CV 260%, point estimate [PE] of the ratio $\mu_{with\ LPV/RTV}/\mu_{without\ LPV/RTV}$ 1.52, 90% confidence interval [CI] 1.24 - 1.86), while the DOR $AUC_{0\text{-}INF}$ fell from 20.1 ng/mL*h (CV 83%) to 10.1 ng /mL*h (CV 66%, PE 0.53, CI 0.45 - 0.62). In volunteers, the DEX $AUC_{0\text{-}INF}$ was barely affected (PE 1.15, CI 0.93 - 1.43) but the DOR $AUC_{0\text{-}INF}$ increased (PE 1.36, CI 1.24 - 1.49), indicating inhibition of CYP3A4 mediated DOR metabolism.

CONCLUSIONS: In HIV infected patients, RTV boosted LPV in steady state decreases the activity of CYP2D6 mediated drug metabolism, while after a single dose in volunteers, inhibition of CYP3A4 seems to predominate.

PI-57

TO EVALUATE THE UTILITY OF SPOT URINE AS AN ALTERNATIVE TO 24 HOUR URINE COLLECTIONS FOR DETERMINATION OF BIOMARKERS OF EXPOSURE IN ADULT SMOKERS IN CONTROLLED SMOKING CONDITIONS. S. Kapur, MD, Q. Liang, PhD, R. Muhammed, MS, H. Roethig, MD, PhD, M. Sarkar, PhD, PMUSA, Richmond, VA.

BACKGROUND: Exposure to cigarettes in adult smokers (SM) is often determined by measuring urinary excretion of selected smoke constituents or metabolites. Complete 24-hour urine (24H) collections are difficult and inconvenient in ambulatory studies, therefore spot urine is often considered as an alternative. The purpose of this study was to determine the optimum time for a spot urine (SU) collection that best reflects a 24H collection.

METHODS: SU samples were collected at three time points (early morning, post-lunch and evening) along with 24H collections in 37 healthy SM . Samples were collected for nicotine and its five metabolites, Nicotine equivalents (NE), metabolites of butadiene (MHBMA), Nitrosamine (NNAL), acrolein (HPMA), benzene (*S*-PMA) and pyrene (1-OHP). Correlation and agreement between creatinine adjusted SU and 24H were determined from the Pearson product-moment correlation, Bland and Altman and Lin's concordance correlation analyses.

RESULTS: There were no significant differences ($p>0.05$) between the three SU collections for all the biomarkers of exposure except for HPMA. The pearson correlation values were (0.66- 0.97) for NE, NNAL, *S*-PMA and MHBMA, and ranged (0.45- 0.82) for 1-OHP and HPMA.

CONCLUSIONS: Spot urine can be used as an alternative to 24 hour urine collections for most of the selected biomarkers. The early morning creatinine adjusted SU appears to be the most feasible and practical option as an alternative to 24H collections.

PI-58

NO PHARMACOKINETIC INTERACTION BETWEEN TRIMETHOPRIM AND PALIPERIDONE ER IN HEALTHY SUBJECTS. A. Cleton, PhD, A. Cleton, K. Talluri, J. Leempoels, A. Thyssen, L. Janssens, M. Eerdekens, S. Boom, Johnson & Johnson, Pharmaceutical Research and Development, Beerse, Belgium.

BACKGROUND/AIMS: Paliperidone is an organic cation and mainly excreted via urinary elimination. This study assessed the effect of trimethoprim (TRI), a potent organic cation inhibitor, on the pharmacokinetics of orally administered Paliperidone Extended Release (ER).

METHODS: This was an open-label, randomised, 2-way crossover study in 30 healthy male subjects. 6 mg Paliperidone ER was administered in the absence of TRI and after 200 mg of TRI was administered b.i.d. for 5 days. The 90% Confidence Interval (CI) of the ratio with/without TRI for PK parameters (Cmax, AUC and amount renally excreted) of Paliperidone were calculated, based on log-transformed data.

RESULTS: Consistent with an inhibition of the active tubular secretion of creatinine by TRI, the creatinine clearance decreased by about 14% (from 119 to 102 mL/min). A slight increase in the fraction unbound (29.7 *vs* 25.7 %), renal clearance (59.2 *vs* 52.4 mL/min), and a slight decrease in total exposure (356 *vs* 391 ng/mL*h) and terminal half-life (21.8 *vs* 26.8 h) of Paliperidone ER was observed. The 90% CIs for the ratios with/without trimethoprim were within the 80-125% for Cmax, AUClast, AUCinf and renal clearance, indicating no effect of TRI on these PK parameters of Paliperidone. The time to maximal concentration and the amount excreted unchanged in urine was not affected by TRI.

CONCLUSION: Co-administration of trimethoprim with a single oral dose of Paliperidone ER did not cause relevant changes in the pharmacokinetic parameters of Paliperidone.

PI-59

ANALYSIS OF THE FLUVOXAMINE-RAMELTEON CYTOCHROME P450 1A2-BASED INTERACTION. C. Collins, MD, R. Levy, PhD, University of Washington, Seattle, WA.

BACKGROUND: Cytochrome 1A2 has received less attention than the other major P450 enzymes in terms of drug interactions. Increases in exposure associated with inhibition of CYP1A2 substrates are generally modest and rarely exceed 10-fold changes in AUC. In 2005, ramelteon was approved for treatment of insomnia. The approved prescribing information indicates that a three day course of fluvoxamine 100 mg twice daily increased the AUC of ramelteon by 190-fold. Since this interaction was attributed to inhibition of CYP1A2, we conducted a two-fold investigation to determine i) whether a precedent exists for AUC increases of 100-fold among CYP1A2 substrates; ii) the spectrum of inhibition interactions associated with fluvoxamine.

METHODS: Data mining utilized the University of Washington Metabolism and Transport Database, approved product labeling and MEDLINE.

RESULTS: The largest AUC increase reported for a therapeutic agent attributed to 1A2 pertains to the interaction between tizanidine and fluvoxamine where 100 mg of fluvoxamine BID for four days increased the AUC of tizanidine 33-fold. Tizanidine is a sensitive 1A2 substrate since ciprofloxacin caused a 7-fold AUC increase.

CONCLUSIONS: The fluvoxamine-ramelteon interaction should not be attributed exclusively to inhibition of 1A2. The unprecedented 190-fold increase in exposure is more likely due to inhibition of all metabolic enzymes involved in the disposition of ramelteon.