PI-53

EFFECTS OF PROPAFENONE ON THE PHARMACOKINETICS OF CAFFEINE. V. Michaud, MSc, M. S. Mouksassi, PharmD, L. Labbé, PhD, P. Bélanger, PhD, M. Lefebvre, MSc, M. Gilbert, MD, O. Grech-Bélanger, PhD, J. Turgeon, PhD, Université de Montréal, Université Laval, Hopital Laval, Université Laval, Montréal, PQ, Canada.

BACKGROUND/AIMS: CYP1A2 is involved in the metabolism of both caffeine and propafenone, a Class Ic antiarrhythmic agent. Despite the widespread consumption of caffeine, drug-drug interactions with this agent are often overlooked. This study investigated effects of propafenone on the pharmacokinetics of caffeine.

METHODS: Eight healthy volunteers were included in a two-phase study. Caffeine (300 mg) was given on two occasions; once alone and once during the coadministration of propafenone (300 mg). Serial blood samples were collected and pharmacokinetic parameters were estimated using a population pharmacokinetic approach.

RESULTS: A one-compartment PK model with first order absorption and elimination described caffeine data. Clearance of caffeine was significantly altered by the coadministration of propafenone; a decrease from 8.3±0.9 L/h to 5.4±0.7 L/h was observed for the oral clearance. Elimination half-life of caffeine was also increased 55% by propafenone. A greater increase in plasma levels of caffeine was observed during coadministration of propafenone in a poor metabolizer of CYP2D6. These results support the concept of competitive inhibition between caffeine and propafenone.

CONCLUSIONS: Propafenone causes significant inhibition of CYP1A2 activity. Caffeine is associated with supraventricular tachycardia; thus, its co-administration with an antiarrhythmic agent such as propafenone should be used with caution especially in patients with poor CYP2D6 activity.

PI-54

PHARMACOKINETIC FACTORS ASSOCIATED WITH TEMPORAL PHARMACODYNAMICS OF T REGULATORY LYMPHOCYTES DURING IMMUNOSUPPRESSIVE THERAPY. K. M. Tornatore, PharmD, K. A. Gillis, PharmD, K. Dole, PharmD, N. Leca, MD, S. Yassa, MD, P. Wallace, PhD, R. C. Venuto, MD, School of Pharmacy & Pharmaceutical Sciences, Novartis Pharmaceuticals Corporation, School of Medicine & Biomedical Sciences, Roswell Park Cancer Institute, School of Medicine & Biomedical Sciences, University at Buffalo, Buffalo, NY.

BACKGROUND/AIMS: Cyclosporine (CYA) pharmacokinetics (PK) and its relationship to T regulatory lymphocytes (Tregs) pharmacodynamics (PD) are unknown. Our objective was to examine CYA PK and PD of Tregs in renal transplant recipients (RTR) during immunosuppressive therapy (IT).

METHODS: 30 male RTR {15 African American (AA); 15 Caucasians (C)} on CYA, mycophenolate mofetil (MMF) and prednisone completed a 12 hour PK-PD study. LC/MSMS analyzed CYA and WINNONLIN generated CYA PK. Lymphocyte sub-populations (LSP) including Tregs (CD4+CD25+, CD8+CD25+) were collected at 0-hr [prior to IT] and 4-hrs after IT and were analyzed by flow cytometry. General Linear Modeling was used to examine variables {CYA Clearance, CYA AUC, prednisone, MMF dose, race, baseline Tregs {0Tregs}) on LSP change.

RESULTS: Decline in all LSP was observed with: CD4+CD25+ {0 hrs: 359 ± 148 to 4 hrs: 242 ± 122 cells/uL; $p<0.05$) and CD8+CD25+ (0 hrs: 26 ± 23 to 4 hrs: 15 ± 11cell/uL; $p<0.05$). Decline in absolute cells and percent change for LSP ($p<0.05$) PD was found with no racial influence. A racial difference in CYA clearance (CL) was noted (CL AA = 7.6 1.9 ml/min/kg vs. CL C = 9.3 4.3 ml/min/kg; p = 0.027). CYA CL and 0Tregs were main effects on decline of CD4+CD25+ (CL:$p=0.006$; 0Tregs: $p=0.0001$) and CD8+CD25+ (CL:$p=0.002$; 0Tregs:$p=0.0001$). An interactive effect between race and prednisone ($p<0.05$) was noted.

CONCLUSION: This PK-PD study indicates that an important relationship between CYA exposure and LSP PD exists which may advance IT monitoring.

PI-55

POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF FEBUXOSTAT IN A PHASE-III STUDY OF PATIENTS WITH GOUT. R. Khosravan, PhD, J. Wu, PhD, N. Joseph-Ridge, MD, L. Vernillet, PharmD, PhD, TAP Pharmaceutical Products Inc, Lake Forest, IL.

AIMS: The objective of this study was to evaluate the population (pop) PK and PD of febuxostat (FBX), a non-purine selective inhibitor of xanthine oxidase, in gout patients and to identify fixed effect sources of variability.

METHODS: In a Phase III, double-blind, 28-week study (N=1072), a subgroup (115Male/10Female) of gout patients receiving 80, 120, or 240 mg of FBX once daily were evaluated for pop PK-PD. Steady-state trough and sparse post dose blood samples were collected from Week 16-24. FBX pop PK and PD [serum uric acid (sUA)] was assessed using NONMEM/XPOSE/SPLUS, including GAM analyses followed by a stepwise selection/elimination process for covariate screening. External validation was done using PK and PD data from a prior Phase II study in gout patients.

RESULTS: Parameter pop means in the final simultaneous pop PK-PD model (FO method) were:

Type	PK-PD Model (2-compartment with indirect response)
PK	$Cl/F = 4.93^{a} + 0.0142*CrCl^{b} + 0.0155*WT^{c} - 1.23*FIB^{d}$ L/h; $V_c/F = 32.2$ L; $V_p/F = 22.2$ L; $t_{lag} = 0.23$ h; $K_a = 13.7^{e}$ h^{-1}; Residual CV = 71%
PD	$K_{in} = 0.0462 + 0.0211*BUA^{f}$ mg/dL/h; $EC_{50} = 0.239^{g}$ μg/mL; $K_{out} = 0.0255$ h^{-1}; Residual SD = 0.863 mg/dL

[a]CV=18%; [b]baseline creatinine clearance in mL/min; [c]total body weight in kg; [d]fibrates (no=0, yes=1); [e]CV=176%; [f]BUA: baseline sUA in mg/dL; [g]CV=67%.

The covariate analyses identified CrCl, WT, and FIB for Cl/F and BUA for K_{in} as statistically significant ($p<0.001$) covariates. External validation results indicated that the inclusion of the covariates for Cl/F in the final model did not improve the bias/precision of the predicted PK parameters/concentrations.

CONCLUSION: A simplified version of the final simultaneous PK-PD model with no covariates for Cl/F is suggested to be as effective in predicting the PK and PD parameters/concentrations in gout patients.