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EFFECT OF RENAL INSUFFICIENCY ON THE PHARMACOKINETICS OF MK-0431 (SITAGLIPTIN), A SELECTIVE DIPEPTIDYL-PEPTIDASE-IV (DPP-IV) INHIBITOR. A. J. Bergman, PhD, J. Cote, BS, B. Yi, PhD, A. Q. Wang, PhD, W. Zeng, MS, L. Chen, MS, T. Marbury, MD, S. Swan, MD, W. Smith, MD, K. M. Gottesdiener, MD, J. A. Wagner, MD, PhD, G. A. Herman, MD, Merck & Co., Inc., Orlando Clinical Research Center, DaVita Clinical Research, New Orleans Center for Clinical Research, West Point, PA.

BACKGROUND/AIMS: This study was conducted to evaluate the influence of renal insufficiency (RI) on the pharmacokinetics (PK) of sitagliptin (SIT), a selective DPP-IV inhibitor in Phase III development for the treatment of type 2 diabetes.

METHODS: 6 patients/subjects in each of the following groups: mild RI (creatinine clearance (CrCl) = 50 to 80 mL/min), moderate RI (CrCl = 30 to 50 mL/min), severe RI (CrCl < 30 mL/min) and healthy subjects (CrCl > 80 mL/min). Each group received a single oral 50-mg dose of SIT. End-stage renal disease (ESRD) patients received 2 single oral 50-mg doses (hemodialysis 4-hr or 48-hr postdose). SIT PK in RI patients was compared to concurrent and historical control subjects. Less than 2-fold increases in $AUC_{0-\infty}$ were not considered clinically meaningful changes.

RESULTS: SIT $AUC_{0-\infty}$ was approximately inversely related to CrCl. Renal clearance (Cl_R) was approximately proportional to CrCl. $AUC_{0-\infty}$ increased less than 2-fold for CrCl > 50 mL/min. $AUC_{0-\infty}$ was 1.6, 2.3, 3.8 and 4.5-fold higher in mild RI, moderate RI, severe RI and ESRD patients, respectively, compared to healthy subjects. C_{max} was 1.4, 1.4, 1.8 and 1.4 higher in mild moderate and severe RI and ESRD, respectively. Dialysis removed ~13.5% of the dose. SIT was well tolerated in all groups.

CONCLUSIONS: Mild RI patients do not require dose-adjustment. To obtain an exposure of SIT similar to patients without renal insufficiency, moderate RI, and severe RI and ESRD patients should receive ½ and ¼ of the usual SIT dose, respectively.

PIII-61

EXENATIDE DOES NOT AFFECT THE PHARMACOKINETICS AND PHARMACODYNAMICS OF WARFARIN IN HEALTHY MALE SUBJECTS. D. Soon, P. Kothare, H. Linnebjerg, S. Park, E. Yuen, K. Mace, C. Chan, S. D. Wise, Eli Lilly and Company, Singapore, Singapore.

BACKGROUND/AIMS: Exenatide, a new therapy for the treatment of type 2 diabetes, slows gastric emptying as one of its actions and therefore may alter the absorption of concomitant oral drugs. This study evaluated the influence of exenatide co-administration on the PK and PD of warfarin.

METHODS: 15 healthy male subjects (22-50 yr, BMI 19.0-27.5 kg/m^2) participated in this open-label, two-period, fixed-sequence study. Each subject received a single, 25-mg, oral dose of warfarin in Period 1 and concomitantly with 10 μg exenatide SC BID in Period 2. Serial sampling for plasma warfarin concentrations and coagulation index (INR) were conducted up to 144 hr post dose.

RESULTS: Exenatide did not produce statistically significant changes in R- or S-warfarin $AUC_{0-\infty}$ or C_{max}. For R-warfarin, the ratios (exenatide/no exenatide) of $AUC_{0-\infty}$ and C_{max} geometric means (90% CI) were 1.11 (1.06-1.17) and 1.05 (1.00-1.09) respectively and for S-warfarin, 1.06 (1.01-1.11) and 0.97 (0.93-1.01). Exenatide also produced no significant changes in INR_{AUC} or INR_{max}; the ratios of geometric means were 0.94 (0.93-0.96) and 0.88 (0.84-0.92) respectively. The most frequent adverse events were mild to moderate nausea, somnolence, and headache; no hypoglycemic events occurred.

CONCLUSIONS: Co-administration of warfarin with exenatide was generally well tolerated and resulted in no significant changes in warfarin PK or in INR. These results indicate that no adjustment in INR monitoring or warfarin dosage is required with exenatide.

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METABOLISM OF ERLOTINIB, AN EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR, BY HUMAN CYTOCHROME P-450 CYP3A4, 3A5, 1A1, AND 1A2. J. Li, PhD, M. Zhao, PhD, S. D. Baker, PharmD, PhD, Johns Hopkins University, Baltimore, MD.

BACKGROUND: Erlotinib (E), an EGFR inhibitor, is approved for the treatment of non-small cell lung cancer. E is extensively metabolized and exhibits wide inter-subject pharmacokinetic (PK) variability. The objective was to characterize E metabolism by human CYP enzymes.

METHODS: E (1.5-50 μM) was incubated with recombinant human CYP3A4, 3A5, 3A7, 1A1, 1A2, and 1B1 (10-160 pmol/ml) at 37^0C for 30 min. E and metabolites were monitored by HPLC with PDA detector. Enzyme kinetics was examined by fitting substrate concentration-reaction velocity curve to Hill equation or Michealis-Menten function using WinNonlin.

RESULTS: E was metabolized primarily by CYP3A4, 3A5, and 1A1, to a lesser extent by 1A2, and to a negligible extent by 3A7 and 1B1. Values for maximum clearance (CL_{max}), representing overall E metabolism, were 0.24, 0.21, 0.31, and 0.15 ml/min/nmol P450 for reactions with CYP3A4, 3A5, 1A1, and 1A2, respectively. The formation kinetics of OSI-420, a main and active *in vivo* metabolite of E, were characterized by assessment of intrinsic clearance (CL_{int}); values were 0.09, 0.05, 0.02, and 0.03 ml/min/nmol P450 for reactions with CYP3A4, 3A5, 1A1, and 1A2, respectively.

CONCLUSIONS: In addition to CYP3A4, 3A5 and 1A1 have significant metabolic capability for overall E metabolism. In smokers, induction of hepatic and/or intratumoral CYP1A1 may represent a predominant elimination pathway for E. Polymorphisms in CYP3A4/5 and CYP1A1 and smoking status may contribute to E PK variability and treatment outcome.

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THE CANNABINOID CANNABIDIOL INHIBITS P-GLYCOPROTEIN ACTIVITY. H. J. Zhu, PhD, J. S. Wang, MD, PhD, J. S. Markowitz, PharmD, J. L. Donovan, PhD, B. B. Gibson, BS, H. A. Gefroh, MS, L. C. DeVane, PharmD, Medical University of South Carolina, Charleston, SC.

AIMS: The purpose of this study was to investigate the possible interaction of P-gp and each of four major marijuana constituents (THC, THC-COOH, CBN and CBD).

METHODS: ATPase activity assay was conducted for measuring the cannabinoids binding affinity for P-gp. LLC-PK1/MDR1 cells and caco-2 cells were used to evaluate the effect of CBD on the uptake of P-gp substrates rhodamine 123 (Rh123) and doxorubicin (DOX). The effects of CBD on the transport of Rh123 across caco-2 and primary cultured rat brain microvessels cells (RBMECs) monolayers were studied in both the basal to apical (B-A) and the apical to basal (A-B) directions.

RESULTS: The data of the P-gp ATPase showed that all four cannabinoids stimulated P-gp ATPase activity. Furthermore, CBD showed a concentration-dependent inhibitory effect on the verapamil stimulated ATPase activity with an IC_{50} value of 39.6μM. At concentrations ranging from 5μM to 100μM, CBD robustly enhanced the intracellular accumulation of Rh123 and DOX. Following exposure to CBD, the transport rate of Rh123 was significantly decreased in B-A directions, but increased in A-B directions. Compared with the control group, the ratios of P_{app} of B-A and A-B directions were dramatically decreased in both caco-2 and RBMECs cells in the presence of 30μM of CBD.

CONCLUSION: These findings indicate that CBD inhibits P-gp-mediated drug transport, suggesting CBD could potentially influence the absorption and disposition of other coadministered compounds that are P-gp substrates.