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THE INFLUENCE OF RENAL IMPAIRMENT ON THE PHARMACOKINETICS OF VILDAGLIPTIN. Y. L. He, PhD, B. Flannery, BS, Y. Wang, J. Campestrini, PhD, M. Ligueros-Saylan, MD, W. P. Dole, MD, D. Howard, PhD, Novartis, Novartis, Novartis, Cambridge, MA.

BACKGROUND: Vildagliptin is a potent and selective DPP-4 inhibitor in clinical development for the treatment of type 2 diabetes. The major elimination pathway is hydrolysis and 23% of an oral dose is excreted as parent in the urine. Kidney is also demonstrated to be one of the major organs that contributes to the hydrolysis metabolism. The objective of this study was to investigate the influence of renal impairment (RI) on the pharmacokinetics (PK) of Vildagliptin.

METHODS: The PK of Vildagliptin was determined in subjects with mild (GFR = 50–80mL/min), moderate (GFR = 30–50 mL/min), severe (GFR < 30 mL/min) renal impairment (RI), and subjects with end stage renal disease (ESRD), compared to subjects with normal renal function (HV) matched for age, gender and body weight. Each group consisted of 6 subjects. Each subject received a single oral dose of 100 mg Vildagliptin. Blood samples were collected to determine plasma concentrations of Vildagliptin and its major inactive metabolite (LAY151) with LC-MS/MS.

RESULTS: Compared to HV, exposure to vildagliptin in subjects with various degrees of RI and ESRD was increased (C_{max}:8–66%; $AUC_{0-\infty}$:32–134%). There was considerable variability in the C_{max} and $AUC_{0-\infty}$ among groups. Renal clearance (CL_R) in HV was 12.4 L/h, and a reduction in CL_R was observed in subjects with RI, which also correlated with the GFR ($R^2 = 0.75$). In contrast, the increase in exposure ($AUC_{0-\infty}$) or CL/F of vildagliptin in RI (average 70% for all subjects with RI) did not correlate with the GFR. Exposure to the inactive metabolite (LAY151) increased in subjects with RI and the magnitude of increase in the exposure was correlated with the severity of RI.

CONCLUSION: The changes in exposure to vildagliptin does not correlate with GFR, and the average increase was less than 2-fold when pooled all subjects with RI. Dose adjustment for vildagliptin is not considered necessary for subjects with RI, and this is further supported by the clinical safety data in long term trials.

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PHARMACOKINETIC COMPARISON OF EXTENDED-AND IMMEDIATE-RELEASE ORAL FORMULATIONS OF SIMVASTATIN IN HEALTHY KOREANS. S. Jang, BS, J. Choi, MD, PhD, M. Park, MD, K. Kim, MD, PhD, K. Park, PhD, MD, Yonsei University College of Medicine, Seoul, Republic of Korea. Supported by Brain Korea 21 Project for Medical Science, Yonsei University.

BACKGROUND: An extended-release (ER) formulation of simvastatin would be expected to have more efficient hepatic uptake by sustained delivery of the drug to the liver. This study compared the pharmacokinetics of ER and immediate-release (IR) formulations of simvastatin after multiple-dose given in healthy subjects.

METHODS: This was designed as a randomized, multiple-dose, parallel study. 29 subjects were randomly assigned to the newly-developed test-formulation (ER, n = 15) and reference-formulation (IR, n = 14) of simvastatin. Each subject received an oral dose of 40 mg every morning for 8 consecutive days. Blood samples were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 13, 17, 24 hours after dosing on day 1 and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 13, 17, 24, 36 and 48 hours after dosing on day 8. Plasma concentrations were analyzed by the LC/MS/MS method, and AUC_{last} (AUC from dosing to the last sample time), C_{max}, t_{max}, and $t_{1/2}$ were determined by a non-compartment method using WinNonlin, for both simvastatin and simvastatin acid.

RESULTS: For simvastatin acid, which is the active compound of the drug, for day 1, AUC_{last}, C_{max}, t_{max} for ER vs IR formulation were on the average 23.2 vs 31.2 ng·hr/ml, 2.2 vs 4.5 ng/ml, and 8.7 vs 4.0 hr, respectively, and for day 8, AUC_{last}, C_{max}, t_{max}, $t_{1/2}$ for ER vs IR formulation were on the average 57.6 vs 41.4 ng·hr/ml, 3.4 vs 5.2 ng/ml, 8.4 vs 4.6 hr, 13.1 vs 4.5 hr, respectively. These results show that the ER formulation has smaller C_{max}, later t_{max} and longer $t_{1/2}$ compared with the IR formulation, reflecting the ideal characteristics of slow-release formulation. Although not statistically significant ($p = 0.2256$), AUC_{last} for the ER formulation for day 8 was larger than IR while it was smaller for day 1, which may be caused by a parallel design of using different subjects for two groups, yielding considerable interindividual variation. The results with simvastatin were similar with simvastatin acid.

CONCLUSION: This study shows that the new ER formulation of simvastatin may have ideal characteristics of slow-release formulation in most of the noncompartmental pharmacokinetic measures in Korean populations. To better evaluate the characteristics of the ER formulation, integrated results including more subjects' kinetic data as well as dynamic data may be needed.

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PHARMACOKINETIC INTERACTIONS BETWEEN RANOLAZINE AND HMG-CoA REDUCTASE INHIBITORS IN VITRO AND IN VIVO. M. Jerling, MD, PhD, CV Therapeutics, Palo Alto, CA.

BACKGROUND/AIMS: Ranolazine is approved by the FDA for the treatment of chronic angina in combination with amlodipine, beta blockers or nitrates, in patients who have not achieved adequate response with other antianginals. It is a CYP3A and P-glycoprotein (Pgp) substrate. The kinetic interactions with the HMG-CoA reductase inhibitors atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin was evaluated in vitro, and the interaction with simvastatin in healthy volunteers.

METHODS: HMG-CoA reductase inhibitors were incubated with human liver microsomes with quantification of parent compound and metabolites. Inhibition constants for ranolazine in these assays were determined. In the clinical study 18 healthy volunteers received a single 80 mg simvastatin dose on Day 1, ranolazine 1750 mg in the morning of Day 3 followed by 1000 mg bid up to Day 9, and simvastatin 80 mg qd Days 6–9. AUC0-∞ after the first simvastatin dose and AUCτ on Day 9 at steady-state were compared for simvastatin lactone, simvastatin acid, 6′-exomethylenesimvastatin, 3′-hydroxysimvastatin, and HMG-CoA reductase inhibitor activity.

RESULTS: In the microsomal assays ranolazine weakly inhibited CYP450-dependent metabolism of all statins except pravastatin with Ki values >20 μM and IC50 values >46 μM. Simvastatin had the highest intrinsic clearance. All statins except pravastatin were Pgp substrates where the difference between basal-to-apical and apical-to-basal transport was lowest for atorvastatin and similar for the other statins. Ranolazine inhibited Pgp-mediated transport of all statins except pravastatin across MDCK-MDR1 cell monolayers with the lowest IC50 value of 39.5 μM for simvastatin. In humans ranolazine increased AUC 1.59-fold for simvastatin lactone (90% CI 1.37–1.84), 1.39-fold for simvastatin acid (1.14–1.71), 1.32-fold for 6′-exomethylenesimvastatin (1.04–1.67), and 1.59-fold for HMG-CoA reductase inhibitor activity (1.45–1.74). AUC decreased for 3′-hydroxysimvastatin.

CONCLUSION: In vitro results indicate that simvastatin is the statin most sensitive to interactions with ranolazine through CYP3A and Pgp inhibition. Ranolazine at the maximum labeled dose increased AUC for simvastatin compounds and HMG-CoA reductase inhibitor activity less than 1.6-fold in humans.

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EARLY MORNING SPOT URINE VOID IS AN IDEAL ALTERNATIVE TO 24 HOUR URINE COLLECTION FOR DETERMINATION OF BIOMARKERS OF EXPOSURE IN ADULT SMOKERS. S. Kapur, S. Mohamadi, R. Muhammad, R. Serafin, Q. Liang, S. Feng, H. Roethig, PM USA, Richmond, VA.

BACKGROUND: Cigarette smoke exposure in adult smokers (SM) can be determined by measuring urinary excretion of selected smoke constituents or metabolites. Complete 24-hour urine (24H)