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MULTIPLE DOSE ADMINISTRATION OF MK-0431 (SITAGLIPTIN), AN INHIBITOR OF DIPEPTIDYL PEPTIDASE-IV, DOES NOT MEANINGFULLY ALTER THE PLASMA PHARMACOKINETICS OR PHARMACODYNAMICS OF SINGLE DOSES OF WARFARIN. D. Wright, PhD, A. Maes, MS, B. Yi, PhD, A. J. Bergman, PhD, Q. Liu, PhD, K. C. Lasseter, MD, K. M. Gottesdiener, MD, J. A. Wagner, MD, PhD, G. A. Herman, MD, Merck & Co., Inc., SFBC International, Rahway, NJ.

BACKGROUND: Sitagliptin is an orally active, potent and selective DPP-IV inhibitor in Phase III trials for the treatment of type 2 diabetes. DPP-IV inhibitors enhance levels of active GLP-1 and other incretins, facilitating glucose-dependent insulin secretion.

METHODS: 12 healthy young male and female volunteers received a single open-label dose of 30 mg warfarin (Bristol-Myers Squibb Company) on Day 5 during 11 days of once-a-day open-label dosing with sitagliptin 200 mg, or a single open-label dose of 30 mg warfarin on Day 1, in this randomized, multiple-dose, open-label, 2-period, crossover study.

RESULTS: Sitagliptin was generally well tolerated. For S(−) and R(+) warfarin, no statistically significant differences in plasma $AUC_{0-\infty}$ were observed and slight reductions in C_{max} were not considered clinically relevant. Prothrombin time (measured by INR) was not altered.

	Least Squares Mean		GMR (CI)
	Warfarin + MK-0431	Warfarin Alone	Warfarin + MK-0431 / Warfarin Alone
S(−) Warfarin $AUC_{(0-\infty)}$ (μg · hr/mL)	70.7	74.1	0.95 (0.90, 1.02)‡
S(−) Warfarin C_{max} (ng/mL)	1958	2198	0.89 (0.86, 0.92)‡
R(+) Warfarin $AUC_{(0-\infty)}$ (μg · hr/mL)	102.6	103.3	0.99 (0.95, 1.03)‡
R(+) Warfarin C_{max} (ng/mL)	1917	2144	0.89 (0.86, 0.93)‡
INR $AUC_{(0-168hr)}$	260	257	1.01 (0.96, 1.06)¶
INR_{max}	2.27	2.10	1.08 (1.00, 1.17)¶

‡90% CI
¶95% CI

CONCLUSIONS: Sitagliptin is well tolerated. Sitagliptin does not meaningfully alter the single dose pharmacokinetics of warfarin (either R or S enantiomers of warfarin) or the single dose pharmacodynamics of warfarin as assessed by prothrombin time INR. Co-administration of sitagliptin and warfarin to healthy subjects is generally well tolerated and these data do not suggest that dosage adjustment for warfarin is necessary when co-administered with sitagliptin.

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POPULATION PHARMACOKINETICS OF BUPIVACAINE AND ROPIVACAINE IN COMBINED FEMORAL-SCIATIC NERVE BLOCK. M. S. Mouksassi, PharmD, F. Varin, PhD, P. Beaulieu, MD, L. Labbé, PhD, University of Montreal, Montreal, PQ, Canada.

BACKGROUND: The objective of our analysis is to describe the population pharmacokinetic (PK) of bupivacaine (BUP) and ropivacaine (ROP) in combined femoral-sciatic nerve block (CFSB) and to identify factors explaining the large interindividual variability (IIV).

METHODS: A randomized double blind study comparing ROP (n=8) and BUP (n=8) in CFSB for knee arthroplasty was conducted. Sciatic nerve block was performed first by injecting 15 ml of a 0.5% solution of either anesthetic using the Labatt approach; femoral nerve block was then performed with 25 ml using a classical anterior approach. Plasma samples were drawn up to 32 h after the first block. Data analysis was performed with NONMEM. The covariates studied were: age, sex (ROP group only), height, weight, and drugs affecting CYP1A2 or CYP3A4. Covariate effects were also tested with permutation tests.

RESULTS: A two compartment model with first order absorption best described the data of BUP. Presence of a CYP1A2 inducer increased the apparent clearance (CL/F) of BUP by 2.6 folds (34.6 vs. 9.9 L/h; p=0.04). The apparent volume of distribution (Vd/F) of BUP was 71.3 L with an IIV of 65%. For ROP a one compartment model with first order absorption was the best. ROP CL/F was 7.7 L/h with an IIV of 23%. The Vd/F of ROP in men was 1.76 greater than in women (366 vs. 208 L; p=0.028).

CONCLUSIONS: Inducer of CYP1A2 increased BUP metabolism even though this is a minor pathway. For ROP, sex differences in Vd/F was observed.

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DEVELOPMENT OF AN IMMOBILIZED HUMAN ORGANIC CATION TRANSPORTER 1 COLUMN FOR USE IN ON-LINE SCREENING. F. Bighi, R. Yamaguchi, S. Patel, P. Ho, I. W. Wainer, R. Moaddel, NIH/NIA, Baltimore, MD.

BACKGROUND/AIMS: To compare a new column based method for characterization of drug-hOCT1 protein interaction.

METHOD: We have immobilized the hOCT1 protein onto an immobilized artificial membrane stationary phase (IAM), resulting in the hOCT1 (+) IAM column. Initial characterization was carried out on the radio flow detector using frontal displacement chromatography techniques.

RESULTS: The binding affinities of nineteen ligands were determined in this manner and compared to reported IC_{50}/Ki values when available and resulted in a significant correlation with and r^2 of 0.9364 and a P value of 0.0015. The sample compounds included 6 chiral compounds and the method was able to identify enantioselective binding interactions.

CONCLUSION: The successful immobilization of the hOCT1 transporter on the IAM stationary phase has been clearly demonstrated. This method allowed the identification of a high affinity binding site for MPP for the first time. We have also shown that the transporter is enantioselective. Future studies will be conducted to determine the effect of certain mutations on binding to the hOCT1 transporter. This method can be easily adapted to other members of this family including but not limited to hOCT2, hOCT3, hOCTN1, hOCTN2 and OAT.