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EXTENSIVE EVALUATION OF GENETIC POLYMORPHISM OF CYP2C19 IN A KOREAN POPULATION: INTERETHNIC COMPARISON AMONG ASIAN POPULATIONS. J. Lee, BS, Y. Yoon, MD, PhD, H. Jeong, MS, S. Lee, PhD, K. Liu, PhD, W. Kang, PhD, I. Cha, MD, PhD, J. Shin, MD, PhD, Inje University, Busan, Republic of Korea.

We evaluated the frequency distribution of the cytochrome P450 2C19 (CYP2C19) allelic variants in a Korean population and also measured the metabolic ratio of omeprazole, a probe drug for CYP2C19 according to the genotypes. The results were compared with those of other ethnics including Vietnamese data which we had studied. Genotyping of CYP2C19 (*2 and *3) was carried out in 282 Korean subjects using PCR-RFLP and ninety-four subjects were participated in phenotyping study using omeprazole. Plasma concentrations of omeprazole and its metabolite, hydroxy-omeprazole were measured at 2hr after 20mg omeprazole intake. Forty subjects were identified to have CYP2C19 genotype of PM with the frequency of 8.9% CYP2C19*2/*2, 3.9% CYP2C192/*3, and 1.4% CYP2C19*3/*3, while 242 Korean subjects carried extensive metabolizer (EM) genotypes which consists of CYP2C19*1/*1 (41.8%), CYP2C19*1/*2 (35.5%), and CYP2C19*1/*3 (8.5%). The frequency distribution of metabolic ratio was distinctly bimodal. Ten Korean subjects were identified to be PMs with an antimode of 1.2. The frequency (12.6 %) of PM in Korean population is significantly higher than those in Vietnamese (7.1 %) and Thai (6.5), but lower than those in Chinese (19.8 %), Filipinos (22.6 %) and Japanese (18.8%).

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WHEN SHOULD URINE SAMPLES FOR NAT2 PHENOTYPING WITH CAFFEINE BE COLLECTED? A. Jetter, MD, M. Kinzig-Schippers, PhD, M. Illauer, BSc., D. Tomalik-Scharte, BSc., F. Sörgel, PhD, U. Fuhr, MD, University of Cologne, Institute for Biomedical and Pharmaceutical Research, Cologne, Germany.

For N-acetyltransferase type 2 (NAT2) phenotyping, urinary ratios of caffeine metabolites are determined after a caffeine test dose. It is not known how these ratios change with postdose time, and which urine collection interval is best for phenotyping.

Therefore, 16 healthy male Caucasians collected urine before and 0-2, 2-4, 4-6, 6-8, 8-12, 12-16, and 16-24 h after a 150 mg caffeine test dose. The test was repeated after 10 days. Concentrations of 5-acetylamino-6-formylamino-3-methyluracil (AFMU), 5-acetylamino-6-amino-3-methyluracil (AAMU), 1-methylxanthine (1X) and 1-methylurate (1U) were measured with LC-MS/MS (LOQ, 100 ng/mL). As a NAT2 metric, the molar ratio (AFMU+AAMU)/(1X+1U+AFMU+AAMU) was determined.

In both periods, urinary ratios were stable from 4 until 24 hours postdose. The arithmetic means for the collection periods ranged from 0.152 to 0.169 and from 0.163 and 0.186, respectively, the CV was <6 % in all cases. Intraindividual CVs were between 9 and 16 % starting 4 hours postdose, while interindividual variability reached values between 58 and 66 %, respectively. There was no statistically significant difference in CV between the respective collection periods or between study periods. Hence, urine for NAT2 phenotyping may be collected at any time between 4 and 24 hours after caffeine dosing. The low intraindividual CVs enable the conductance of interaction studies assessing the effect of drugs on NAT2 activity with a sample size as low as $n=12$ subjects.

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TISSUE BIOPSY TECHNIQUES FOR GENE-EXPRESSION PROFILING IN CLINICAL PHARMACOLOGY. M. van Doorn, MD, M. Kemme, MD, PhD, A. Cohen, MD, PhD, E. van Hoogdalem, PhD, K. Burggraaf, MD, PhD, Centre for Human Drug Research, Leiden, Netherlands.

Gene-expression profiling studies require sufficient quality/quantity mRNA to obtain valid results. In animal studies, obtaining relevant tissue material is not a problem, but in humans there are obvious constraints. Therefore, we evalauted tissue biopsy techniques, perceived burden and the RNA extraction methods in 12 healthy subjects.

On a single day a muscle and fat biopsy were done and a 10ml blood sample was taken, followed by follow-up visits after 3 and 7 days. Abdominal sc adipose tissue was sampled with a suction technique after local anaesthesia. Muscle tissue was sampled with a modified Bergström needle from the quadriceps muscle under sterile conditions and local anaesthesia. Tolerability was assessed with questionnaires directly after the procedure and at follow-up visits.

The procedures were well tolerated by all subjects. The fat biospy was associated with none to minimal discomfort both during the procedure and during follow-up. The discomfort of the muscle biopsy was rated as comparable to the venepuncture. At follow-up a mild bruise-like feeling for a median time of 48 hrs was reported.

The average and (range) RNA yield of the leucocytes was 13 (2.3-28.8) μg. On average 237 (79-353) mg muscle tissue was sampled. Half of each sample was analysed for RNA quantity, yielding on average 16.9 (4.1-41.8) μg RNA. From the average 197 (61-430) mg adipose tissue 3.9 (1.4-8.5) μg RNA could be obtained. RNA from all samples was of good quality. Gene-expression profiling with the material showed significant associations between anthropometric variables and genes involved in glucose homeostasis. Thus, tissue sampling in human is feasible and can be used for gene-expression profiling clinical pharmacology studies.

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CYP GENOTYPES INFLUENCE THE EFFECT OF TAMOXIFEN THERAPY ON SERUM LIPIDS. M. I. Rehman, MD, K. Lee, MD, PhD, A. Bermes, BSc, T. Skaar, PhD, M. Arefayene, L. Li, PhD, V. Stearns, MD, D. F. Hayes, MD, D. A. Flockhart, MD, PhD, Indiana University School of Medicine, Sungkyunkwan University School of Medicine, Johns Hopkins University, University of Michigan, Indianapolis, IN.

Beneficial effects of tamoxifen therapy on LDL-cholesterol have been reported in several studies. We examined the relationship between genetic polymorphisms in CYP2D6 (*1, *4, *5, *6 and *10) and CYP2C9 (*1, *2 and *3) genes and serum lipid profile in 28 women who took tamoxifen (20mg/day) for the management of breast cancer. The fasting serum lipid profiles were evaluated before starting tamoxifen therapy and at the end of four months of treatment. The total and LDL-cholesterol lowering effect of tamoxifen was not significantly different among groups carrying different CYP2D6 genotype variants. The same was true for CYP2C9 groups. A significant decrease in total and LDL-cholesterol was noted in women who carried a combination of *1/*1 variants of CYP2D6 and CYP2C9 genes or a combination including *1/*1of either CYP combined with any other variant of the other CYP ($p=0.0003$ and 0.0001 for total and LDL cholesterol respectively). CYP2D6 *1/*10 combined with a heterozygous variant of CYP2C9 did not adversely influence the beneficial effect of tamoxifen consistent with the *10 variant only partially decreasing enzyme activity. No beneficial effect of tamoxifen was seen in the group of patients who carried variants of both CYPs. The use of new multi-comparison algorithms to evaluate the effects of multiple genetic variants on robust measures of drug response is critical to the demonstration of predictive pharmacogenetic patterns.