FMO Phenotypes Obtained by Ranitidine *N*-Oxidation is Correlated with *FMO3* Genotypes in Korean Population

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A non-invasive method of determining FMO3 activity catalyzing ranitidine (RA) *N*-oxidation was developed and used to phenotype 210 Korean volunteers (173 males and 37 females, 110 non-smokers and 100 smokers). Amounts of RA and its *N*-oxide metabolite (RANO) in 8 hr urine were determined using HPLC. Urinary molar ratio of RA/RANO was used as a reciprocal index of FMO activity. Distribution of the ratio showed trimodality; 13 subjects (6%) were slow *N*-oxidizers (ratio range was 17.5 to 27.2), 105 (50%) were intermediate (9.7 to 15.6) and 92 (44%) were fast (5.6 to 9.6) *N*-oxidizers. Blood samples were collected and genomic DNAs were analyzed for the 3 previously found FMO3 mutant alleles (C442T, G472A and A923G producing respectively FMO3/Stop^{148}, Lys^{158} and Gly^{308}) in our Korean population. Heterozygotic Stop^{148} codon was detected in one intermediate *N*-oxidizers. Volunteers (n=69) who were homozygous or heterozygous for either one or both of the FMO3/Lys^{158} and FMO3/Gly^{308} mutations had significantly lower *in vivo* FMO activities (higher RA/RANO ratio) than those with homozygous wild type alleles (n=141) ($p<0.001$). Among 13 putative slow *N*-oxidizers, 9 subjects were either homozygous or heterozygous for both Lys^{158} and Gly^{308} mutations. However, the remaining 4 subjects carried homozygous wild type alleles in both sites, indicating that there are still unidentified mutants in *FMO3* gene which affect RA *N*-oxidation (FMO3) activity in Korean population. Combined, these results suggest that the 2 point mutations found commonly in *FMO3* gene in Korean population are highly correlated with FMO polymorphism determined with RA *N*-oxidation. Thus, the Koreans with these *FMO3* mutations may have altered pharmacokinetics for drugs metabolized primarily by hepatic *FMO3*.