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Variability in carcinogen metabolism

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Cigarette smoke consists of thousands of constituents. Some of these e.g. 4-aminobiphenyl and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) have been identified by the International Agency for Research on Cancer (IARC) as human carcinogens (IARC Group 1 carcinogens). Exposure to cigarette smoke constituents can occur through many other sources in addition to cigarette smoke. The systemic exposure for these constituents depends primarily on their absorption, distribution, metabolism and excretion (ADME). Of the ADME processes, metabolic activation and detoxification plays a significant role in determining the systemic exposure. A substantial proportion of the differences in metabolism can be accounted by induction or inhibition as well as genetic polymorphisms of the metabolic enzymes. There is abundant evidence on the allelic variants for the different enzymes involved in the metabolism of these carcinogens. The tobacco specific nitrosamine, NNK undergoes carbonyl reduction to NNAL (4-methylnitrosamino-1-(3-pyridyl)-1-butanol) by the CYP450 enzyme, CYP2A6, that exhibits genetic polymorphisms. NNAL undergoes subsequent glucuronidation through the glucuronyl transferases, UGT1A4 and UGT2B10. The UGT2B10 Asp67Tyr allele has been linked to a haplotype associated with decreased N-glucuronidation of NNAL. Similarly, allelic differences in CYP1A2 and N-acetyltransferase enzymes have also been attributed to variations in 4-aminobiphenyl metabolism. The composite effect of the phenotypic outcome of the individual genotypic differences and its subsequent impact on systemic exposure has not been methodically characterized. Such an assessment is possible by determining the metabolite ratios as well as measuring the overall exposure as estimated from urinary excretion. Data from a stratified, multi-center, cross-sectional study of 3,585 adult smokers and 1,077 non-smokers were analyzed to characterize the variability in carcinogen metabolism. The different sources of variability in carcinogen exposure will be discussed in this presentation.

Biography

Mohamadi Sarkar, M.Pharm., Ph.D., FCCP, serves as Senior Principal Research Scientist for Altria Client Services in Richmond, Virginia, since August 2002. He has authored more than 100 scientific peer-reviewed publications and presentations at scientific meetings. Dr. Sarkar has also participated in several invited seminar presentations and authored a variety of scientific book chapters related to his areas of expertise and won several research and teaching awards. He has held various academic appointments in Clinical Pharmacology at the School of Pharmacy in Virginia Commonwealth University (VCU) as well as West Virginia University. He continues to serve as Affiliate Associate Professor and teach Clinical Pharmacology at VCU.