Letters to the Editor

Correspondence re: S. H. McQuilkin et al., Analysis of Within-Subject Variation of Caffeine Metabolism When Used to Determine Cytochrome P4501A2 and N-Acetyltransferase-2 Activities. Cancer Epidemiol., Biomarkers & Prev., 4: 139–146, 1995

Letter

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The following comments pertain exclusively to the determination of cytochrome CYP1A2 and not to that of N-acetyltransferase 2. With the help of excellent laboratory work and a logically designed experimental procedure, the authors show the level of reproducibility of two caffeine metabolic ratios by repeat investigations in a number of subjects. Unfortunately, this effort is not very useful because the main concern is the interpretation of these metabolic ratios in terms of CYP1A2 activity. We are worried that the widespread adoption of the recommended methods in cancer research would lead to results that are not much better than half truths (see correlation coefficient below). This assessment also fits to the lack of good reproducibility that is shown by McQuilkin et al.

The basis of our concern has been published in specific terms by Tang et al. (1) in a paper not quoted here, and in general terms in a review paper by Kalow and Tang (2), chided by McQuilkin, et al. for not quoting detector sensitivities and other details. Briefly, the main trouble with the Butler methods tested by McQuilkin et al. is the urine-flow-dependent excretion of caffeine so that the interpretation of Butler’s ratio in metabolic terms introduces an error component. Second, the timing of urine collection (4–5 h) is not necessarily proper for all subjects. After population screening, the Butler methods led to claims for bi- or trimodal frequency distribution of CYP1A2 activity, whereas all other methods using caffeine for CYP1A2 determination lead to normal distribution curves within nonsmokers and within groups of heavy smokers, a serious discrepancy for cancer studies.

Systemic caffeine clearance is the best known measurement of CYP1A2 activity in humans. The Butler test correlated with systemic caffeine clearance with a correlation coefficient of only $r = 0.46$ (1). In principle, CYP1A2 assays based on blood tests are best, saliva tests are good if properly done, and urine tests are potentially useful.

References


Reply

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On behalf of my colleagues, I am pleased to respond to the recent letter from Drs. Tang and Kalow about our recent article "Analysis of within-subject variation of caffeine metabolism when used to determine cytochrome P4501A2 and N-acetyltransferase-2 activities." We were pleased that Drs. Tang and Kalow found our work to be logically designed and contributing to the body of knowledge about using this type of technique for determining the phenotype of individuals for these two enzyme systems.

We agree with Drs. Tang and Kalow that any technique that utilizes collection of urine samples for quantitating probe drug and metabolites is by definition dependent upon not only drug metabolism, but also upon relative rates of renal clearance of analytes of interest. This disadvantage (the undesired contribution of renal variation) may be counterbalanced by the advantage that subjects may be more willing to submit one urine specimen (obtained at an appropriate time) than several blood samples obtained over an appropriate time period (necessary to determine AUC and plasma clearance of a probe drug). Systemic caffeine clearance (total plasma clearance of caffeine) will be composed of the sum of all clearance terms, whether renal or hepatic, via several different routes. Therefore, it is not surprising that correlation between measures of total plasma clearance of a probe drug like caffeine and measures of one specific metabolic pathway may be less than perfect.

We appreciate the helpful comments from Drs. Tang and Kalow. Even for a simple probe drug like caffeine, current strategies for determining phenotypes of enzyme activities are less than perfect, and "optimal" assays have probably not yet been defined.
An error occurred in the printing of the February 1996 issue of Cancer Epidemiology, Biomarkers & Prevention involving the placement of two articles by Mary A. Norman et al., “Prenatal Exposure to Tobacco Smoke and Childhood Brain Tumors: Results from the United States West Coast Childhood Brain Tumor Study” and the Review article “Childhood Brain Tumors and Exposure to Tobacco Smoke.” The pages on which these articles appear in the issue do not coincide with the Table of Contents. The Review article appears on pages 85–91, whereas the Table of Contents erroneously lists it as being on pages 127–133. The regular article appears on pages 127–133, whereas the Table of Contents lists it as being on pages 85–91.
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