Letter to the Editor


Fred F. Kadlubar¹, John F. Young, Nicholas P. Lang, Neil E. Caporaso, Rashmi Sinha, and Maria Teresa Landi

National Center for Toxicological Research, Jefferson, Arkansas 72079
[FFK, J. F. Y.]; Arkansas Cancer Research Center, Little Rock, Arkansas 72205 [N. P. L.]; National Cancer Institute, Bethesda, Maryland 20892 [N. E. C., R. S.]; and EPOCA, Epidemiology Research Center, University of Milan, Milan 20122, Italy [M. T. L.]

The following comments pertain exclusively to a Letter to the Editor by B. K. Tang and W. Kalow (1) that concludes that the “Butler methods” developed by our laboratory (2) for determining CYP1A2 activity are inadequate and that adoption of these methods “in cancer research would lead to results that are not much better than half-truths.” Because our method, which measures the urinary molar ratio of (17X + 17U)/137X, and that of Tang and Kalow (3), which uses the urinary ratio of (AAMU + 1X + 1U)/17U, are both being used in a variety of cancer epidemiology and biomarker studies, we again wish to comment on the validity of our original method.

The basis for the conclusions of Tang and Kalow is derived from previous work by these authors (3) in which they reported that caffeine (37X) excretion is urine flow-dependent and that the ratio of (17X + 17U)/137X reflects only a polymorphism in renal clearance of caffeine. We have previously stated (4) that, although caffeine clearance is indeed dependent on urine flow, we could find no evidence that caffeine urinary concentrations are urine flow-dependent under our experimental conditions and methods of analysis. Furthermore, our results agree with those of Birkett and Miners (5), who have also reported that urinary caffeine concentrations are independent of urine flow rate. In a recent study, in which we found comparable trimodal distributions for both the (17X + 17U)/137X ratio and the caffeine breath test, we noted a urinary constituent that often co-migrates with caffeine on a variety of HPLC columns. Moreover, its excretion was highly dependent on urine flow rate. In a recent study, in which we found comparable trimodal distributions for both the (17X + 17U)/137X ratio and the caffeine breath test, we indicated that the use of this constituent for the measurement of caffeine clearance and that the use of other ratios is questionable. We agree with this assessment for 24-h or spot urine samples and again emphasize the need for 4-5 h urine collections for measuring (17X + 17U)/137X. Moreover, this study (7) and others (3, 6) regard caffeine clearance as the gold standard for reflecting CYP1A2 levels in liver. We do not believe that there is any experimental support for this assumption and tend to regard the (3-13C)caffeine breath test (8) as the most direct measure of CYP1A2-catalyzed caffeine 3-demethylation in the liver.

Tang and Kalow further state in their Letter to the Editor “that all other methods using caffeine for CYP1A2 determination lead to normal distribution curves,” whereas we and our collaborateurs have reported bimodal or trimodal distributions. However, Fuhr and Rost (9), who used 17X/137X ratios in plasma and saliva, found bimodal distributions for CYP1A2 activity in both smokers and nonsmokers. These findings are also in accordance with family studies and in vitro metabolism data that have consistently shown a heritable bimodal/trimodal distribution for CYP1A2 activity. Yet these data do not necessarily imply that there must be a functional variant in the CYP1A2 gene (10), since a polymorphic phenotype can arise from mutations in regulatory genes or can be due to individual differences in long-term exposures to agents that alter hepatic CYP1A2 levels.

Most studies to date have used probit plots to depict CYP1A2 phenotypic distributions. However, we wish to stress that probit plots are simply graphical methods that are useful to assign cutoffs and are not statistical tests (11). Perhaps these controversies can be fully resolved by using more accurate...
statistical approaches, by conducting additional family and nutritional epidemiological studies, and by sequencing genes that control CYP1A2 expression or inducibility.

References

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