Letter to the Editor

Endogenous 4β-Hydroxycholesterol-to-Cholesterol Ratio Is Not a Validated Biomarker for the Assessment of CYP3A Activity

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Björkhem-Bergman et al. (2013) published a study in healthy adults evaluating endogenous 4β-hydroxycholesterol-to-cholesterol ratio to measure CYP3A induction. The authors compare CYP3A induction fold-changes and determined correlations between 4β-hydroxycholesterol-to-cholesterol ratio and midazolam clearance after rifampicin administration. Midazolam clearance is a validated biomarker to evaluate CYP3A activity. We commend the authors for attempting to find alternative, simple, and cost-effective methods to evaluate CYP3A activity. However, we are concerned that the study results may lead to inappropriate use of the 4β-hydroxycholesterol-to-cholesterol ratio for evaluating CYP3A-mediated drug-drug interactions.

A statistically significant, but weak, relationship was reported between 4β-hydroxycholesterol-to-cholesterol ratio and midazolam clearance (coefficient of determination \( r^2 = 0.29, P < 0.01 \)). The authors state that the ratio “...might be used as a marker to evaluate CYP3A activity at baseline and not only during induction” (Björkhem-Bergman et al., 2013). Although correlation coefficients \( r \) and/or \( r^2 \) values are commonly reported in the literature and used to assume suitability of a cytochrome P450 (P450) probe (Fuhr et al., 2007), values are not a measure of predictive performance (Sheiner and Beal, 1981; Bland and Altman, 1986). Additional limitations of \( r^2 \) values include the inability to determine if the most appropriate set of independent variables was selected, whether independent variables are causes of changes in the dependent variable, and whether omitted-variable bias exists (Nagelkerke, 1991; Draper and Smith, 1998).

Additionally, in a previously published study, the authors compared 4β-hydroxycholesterol to another validated CYP3A probe, quinine, and reported weak \( r \) values with statistical significance \( r = -0.24 \) to \(-0.5, P < 0.05 \) (Diczfalusy et al., 2008). However, statistically significant \( r \) and/or \( r^2 \) values do not substantiate that a P450 probe is valid for general use. Correlation coefficients and/or coefficients of determination are often overvalued and result in exaggerated conclusions. A P450 probe should adhere to validation criteria to be considered appropriate for use (Watkins, 1994; Zaigler et al., 2000; Fuhr et al., 2007). Given the limitations of \( r \) and \( r^2 \) values in general, as well as in these studies (Diczfalusy et al., 2008; Björkhem-Bergman et al., 2013), we do not believe that the 4β-hydroxycholesterol-to-cholesterol ratio has been validated as a biomarker for the measurement of CYP3A activity.

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References


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