Letters to the Editors

Poor correlation between 6 β -hydroxycortisol:cortisol molar ratios and midazolam clearance as measure of hepatic CYP3A activity: a comment

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I read with great interest the paper of Chen and coworkers [1], who reported on the 'relationship between a validated biomarker, intravenous midazolam clearance and the urinary cortisol ratio under constitutive conditions and with the influence of a moderate CYP3A inhibitor' (p.1). The authors concluded that the 'high intra-individual variability of the urinary cortisol ratio, compared with midazolam, makes this a suboptimal CYP3A phenotyping tool' (p.1). A shortcoming may confound their results making the interpretation of their cortisol ratio difficult, if not impossible: the authors did not pay attention to a possible influence of varying urine volume. This criticism is based on the well-documented relationship between urine volume and urinary free cortisol excretion [2–8]. Unfortunately, the results of Chen *et al.* [1] would not be improved if results were reworked and the volume of each 24-h urine taken into calculation, since urinary steroid excretion depends also on daytime: an increase of urine volume in the morning (zenith of adrenocortical secretion [9]) will have a more pronounced effect on steroid excretion than a similar change of urine flow in the evening (nadir of adrenocortical secretion [9]). Conclusion: urinary free cortisol and probably of 6 β -hydroxycortisol excretion in 24-h urines should be determined only if the urine volume is kept as constant as possible – this demands that patients or volunteers strictly observe their fluid intake (volume, daytime). Future work will then show that the ratio of urinary 6 β -hydroxycortisol/cortisol can be used as an index for CYP3A phenotyping.

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Received

13 July 2006

Accepted

17 July 2006

Published OnlineEarly

10 November 2006

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