

Major comments

- 1) In compliance with the reviewer's request, we added a more detailed description of the determinants of hepatic elimination of drugs with high and low extraction ratio (p.8 , last 5 lines; p. 9, first 2 lines).
- 2) We did not comment on MELD score because, to our knowledge, its predictive value of hepatic drug-metabolizing activity had never been assessed. A PubMed search (performed on August 17, 2015) confirmed that, although widely used at present time to predict survival and the need of transplantation, as well as in non-liver transplant settings such as prognosis of variceal bleeding, infections, alcoholic hepatitis, placement of TIPS and management of fulminant hepatic failure, the MELD score has not yet been used to correlate the degree of liver injury with drug-metabolizing activity. Hence, no useful (evidence-based) comment can be made on its performance as a predictor of drug metabolism in cirrhosis.
- 3) We strived to make this point as clear as possible to readers unfamiliar with pharmacokinetic theory by recalling basic pharmacokinetic principles and describing in greater detail the meaning of experimental observations (p. 23, lines 3-15).

Minor issues

- 4) The reviewer raises an important question. However, as can be seen from refs. 10-12 and 107, *in silico*, *in vitro* and *in vivo* models thus far proposed for a quantitative prediction of the magnitude of DDIs apply only to healthy subjects. Following the reviewer's suggestion, we added a comment on this methodological question (last paragraph of p. 37 to the end; last 4 lines of Abstract).
- 5) The value of extraction ratio for antipyrine and aminopyrine has been added (p. 9, lines 9-11).
- 6) Only the plasma protein binding of the victim drug may be important in determining the magnitude of a pharmacokinetic interaction. The plasma protein binding of quinine (90%) is

specified on p. 21, and its importance in determining the extent of the erythromycin-quinine interaction is discussed in detail (pp. 21-22). Data regarding protein binding of theophylline and lidocaine are not reported since they are not highly-bound drugs (theophylline $56 \pm 4\%$; lidocaine $69 \pm 2\%$ mainly to AAG, ref. 68). Therefore, any possible displacement from their plasma protein-binding sites is not clinically relevant. This is confirmed by two observations: a) contrary to what observed with the highly-bound drug quinine (Table 2), the inhibition by erythromycin of the total plasma clearance of lidocaine does not decrease as AAG concentration (and consequently lidocaine binding) decreases in cirrhotic patients (p. 21, lines 7-12; ref. 46); b) the steady state volume of distribution of lidocaine remains unaltered in the presence of the competing drug erythromycin (ref. 46).

7) Typographical error (missing inter-word space) corrected (p.21, line 1). However, please note that this and many other inter-word spaces are missing in the locked version.